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(21) International Application Number: PCT/US93/04643 (22) International Filing Date: 14 May 1993 (14.05.93) (30) Priority data: 886,572 20 May 1992 (20.05.92) US (60) Parent Application or Grant (63) Related by Continuation US 886,572 (CIP) Filed on 20 May 1992 (20.05.92) (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only): BAKSHI, Raman, K. [IN/US]; 9 Azalea Drive, Edison, NJ 08820 (US); RASMUSSEN, Gary, H. [US/US]; 155 Park Place, Watchung, NJ 07060 (US). TOLMAN, Richard, L. [US/US]; 29 Upper Warren Way, Warren, NJ 07059 (US). PATEL, Gool, F. [US/US]; 60 Nottingham Way, Millington, NJ 07946 (US). HARRIS, Georgianna [US/US]; 43 Parmly Road, Tinton Falls, NJ 07724 (US). GRAHAM, Donald, W. [US/US]; 294 Old Tote Road, Mountain-side, NJ 07092 (US). WITZEL, Bruce, E. [US/US]; 115 Scotch Plains Avenue, Westfield, NJ 07090 (US). (74) Agent: GRASSLER, Frank, P.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: BB, BG, BR, CZ, FI, HU, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: NEW 7 β -SUBSTITUTED-4-AZA-5 α -ANDROSTAN-3-ONES AS 5 α -REDUCTASE INHIBITORS (57) Abstract Described are new 7 β -substituted 4-aza-5 α -androstan-3-ones and related compounds as 5 α -reductase inhibitors.		

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TITLE OF THE INVENTION

NEW 7 β -SUBSTITUTED-4-AZA-5 α -ANDROSTAN-3-ONES AS
5 α -REDUCTASE INHIBITORS

5

BACKGROUND OF THE INVENTION

The present invention is directed to new 7 β -substituted-4-aza-5 α -androstan-3-ones and related compounds and the use of such compounds as 5 α -reductase inhibitors.

10

DESCRIPTION OF THE PRIOR ART

The art reveals that certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, male pattern baldness and benign prostatic hypertrophy, are the result of hyperandrogenic stimulation caused by an excessive accumulation of testosterone or similar androgenic hormones in the metabolic system. Early attempts to provide a chemotherapeutic agent to counter the undesirable results of hyperandrogenicity resulted in the discovery of several steroidal antiandrogens having undesirable hormonal activities of their own. The estrogens, for example, not only counteract the effect of the androgens but have a feminizing effect as well. Non-steroidal antiandrogens have also been developed, for example, 4'-nitro-3'-trifluoromethyl-isobutyranilide. See Neri, et al., Endo., Vol. 91, No. 2 (1972). However, these products, though devoid of hormonal effects, are peripherally active, competing with the natural androgens for receptor sites, and hence have a tendency to feminize a male host or the male fetus of a female host.

It is now known in the art that the principal mediator of androgenic activity in some target organs is 5 α -dihydrotestosterone, and that it is formed locally in the target organ by the action of testosterone-5 α -reductase. It is also known that inhibitors of testosterone-5 α -reductase will serve to prevent or lessen symptoms of hyperandrogenic stimulation.

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A number of 4-aza steroid compounds are known in the art as 5α -reductase inhibitors. For example, See U.S. Patent Nos. 4,377,584, 4,220,775, 4,859,681, 4,760,071 and the articles J. Med. Chem. 27, p. 1690-1701 (1984) and J. Med. Chem. 29, 2998-2315
5 (1986) of Rasmusson, et al., U.S. Patent 4,845,104 to Carlin, et al., and U.S. Patent 4,732,897 to Cainelli, et al. describe 4-aza-17 β -substituted- 5α -androstan-3-ones which are said to be useful in the treatment of DHT-related hyperandrogenic conditions.

However, despite the suggestion in the prior art that
10 hyperandrogenic diseases are the result of a single 5α -reductase, there are reports regarding the presence of other 5α -reductase isozymes in both rats and humans. For example, in human prostate, Bruchovsky, et al. (See J. Clin. Endocrinol. Metab. 67, 806-816, 1988) and Hudson (see J. Steroid Biochem. 26, p 349-353, 1987)
15 found different 5α -reductase activities in the stromal and epithelial fractions. Additionally, Moore and Wilson described two distinct human reductases with peaks of activities at either pH 5.5 or pH 7-9. (See J. Biol. Chem. 251, 19, p. 5895-5900, 1976.)

Recently, Andersson and Russell isolated a cDNA which
20 encodes a rat liver 5α -reductase (see J. Biol. Chem. 264 pp. 16249-55 (1989). They found a single mRNA which encodes both the liver and prostatic reductases of rats. The sequence of this rat gene was later used to select a human prostatic cDNA encoding a 5α -reductase termed " 5α -reductase 1". (See Proc. Nat'l. Acad. Sci. 87, p. 3640-
25 3644, 1990.)

More recently, a second, human prostatic reductase (5α -reductase 2) has been cloned with properties identified with the more abundant form found in crude human prostatic extracts. (See Nature, 354, p. 159-161, 1991.)

30 Further, "Syndromes of Androgen Resistance" - The Biology of Reproduction, Vol. 46, p. 168-173 (1992) by Jean O. Wilson indicates that the 5α -reductase 1 enzyme may be associated with hair follicles.

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Thus, the art supports the existence of at least two genes for 5 α -reductase and two distinct isozymes of 5 α -reductase in humans. Both forms are present in prostatic tissue although 5 α -reductase 2 is the more abundant. The other isozyme, 5 α -reductase 1, is believed to be more abundant in scalp tissue.

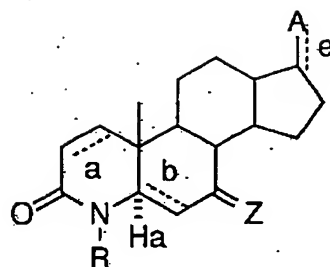
In the treatment of hyperandrogenic disease conditions, e.g. benign prostatic hyperplasia (BPH) it would be desirable to have one drug entity which is active against both isozymes 1 and 2 in the prostate to substantially inhibit dihydrotestosterone (DHT) production. Alternatively, it would be desirable to have a drug entity which is highly selective for inhibiting the scalp-associated enzyme 5 α -reductase 1, for use in treating diseases of the skin and scalp, e.g. acne and alopecia. This latter drug could also be used in combination with PROSCAR® (finasteride) which is highly selective for the prostatic enzyme 5 α -reductase 2 for combination therapy in the treatment of BPH.

SUMMARY OF THE INVENTION

The present invention discloses novel 7 β -substituted-4-aza-5 α -androstan-3-one compounds which are useful for inhibiting the 5 α -reductase isozymes 1 and/or 2 and are particularly effective in selectively inhibiting the 5 α -reductase 1 associated with the scalp and indually inhibiting both isozymes 1 and 2 in the treatment of benign prostatic hyperplasia, acne, female hirsutism, male pattern baldness, androgenic alopecia, prostatitis, and the prevention and treatment of prostatic carcinoma.

In accordance with the present invention there is provided novel 7 β -substituted-4-aza-5 α -androstan-3-one compounds of the formula:

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General Formula I

10 wherein

R is selected from hydrogen, methyl or ethyl; the dashed lines-a, b, e indicate double bonds which can be present, providing that if double bond b is present, then the 5 α hydrogen, Ha, is not present;

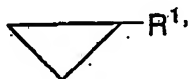
15 Z can be:

1) oxo,

2) a-hydrogen and a β -substituent selected from C₁-C₄ alkyl, C₂-C₄ alkenyl, -CH₂COOH, hydroxy, carboxy, COOC₁-C₄ alkyl esters; OCONR¹R², where R¹ and R² are independently H, C₁-C₄ alkyl, phenyl, benzyl, and where R¹ and R² together with the nitrogen can form a 5-6 membered saturated heterocyclic ring, optionally with one other heteroatom; OC₁-C₄ alkyl, OC₃-C₆ cycloalkyl, -OCOCH₃, halo, halo C₁-C₂ alkyl, or trifluoromethyl, C₃-C₆ cycloalkyl;

3) =CH-R¹ where R¹ is H, C₁-C₄ alkyl;

4) Spiro



30

where R¹ is H, C₁-C₄ alkyl; and

A can be:

O

- 5 -

IA) -C-Q, where Q is:

- 5 (1) NR^2R^3 , where R^3 is independently hydrogen, methyl or ethyl; and R^2 is a hydrocarbon radical, selected from substituted or unsubstituted straight or branched chain alkyl, cycloalkyl, or aralkyl of from 1-12 carbons or monocyclic aryl optionally containing 1 or more lower alkyl substituents of from 1-2 carbon atoms and/or 1 or more halogen substituents, with the proviso that Z is not beta-methyl where R^2 is $\text{C}_1\text{-C}_8$ alkyl;
- 10 (2) a hydrocarbon radical being:
 - (a) a monovalent aliphatic radical selected from straight or branched chain alkyl, or cycloalkyl, of from 1-12 carbons, which can be substituted by one or more of $\text{C}_1\text{-C}_2$ alkyl or halo, excluding $\text{C}_1\text{-C}_4$ alkyl when Z is beta-methyl;
 - 15 (b) an aralkyl radical selected from benzyl or phenethyl;
 - 20 (c) a polycyclic aromatic radical which can be substituted with one or more of: -OH, organosilyl protected -OH, $-\text{OC}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkyl, halo or nitro;
 - (d) a monocyclic aromatic radical which can be substituted with one or more of:
 - 25 (i) -OH, $-\text{OC}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkyl, $-(\text{CH}_2)_m\text{OH}$, $-(\text{CH}_2)_n\text{COOH}$, including organosilyl protected hydroxy, where m is 1-4, n is 1-3, providing $\text{C}_1\text{-C}_4$ alkyl is only present when one of the above oxygen-containing radicals is present;
 - 30 (ii) -SH, $-\text{SC}_1\text{-C}_4$ alkyl, $-\text{SOC}_1\text{-C}_4$ alkyl, $-\text{SO}_2\text{C}_1\text{-C}_4$ alkyl, $-\text{SO}_2\text{N}(\text{C}_1\text{-C}_4\text{-alkyl})_2$, $-\text{SO}_2\text{NH}(\text{C}_1\text{-C}_4\text{alkyl})$, $-(\text{CH}_2)_m\text{SH}$, $-\text{S}-(\text{CH}_2)_n\text{-O-COCH}_3$, where m is 1-4 n is 1-3,

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providing C₁-C₄ alkyl is only present when one of the above sulfur containing radicals is present;

- 5 (iii) N(R³)₂, which can be protected, where R³ is independently H or C₁-C₄ alkyl, where the monoaryl ring can also be further substituted with C₁-C₄ alkyl; and
- 10 (iv) heterocyclic selected from 2-, 3-, or 4-pyridyl, 2-pyrrolyl, 2-furyl or thiophenyl; and

(IIA), where:

A is -XR⁴, or -(CHR¹)_n-XR⁴;

n is 1-10;

15 X is -O- or -S(O)_p-,

wherein p is zero, 1 or 2; and

R¹ can be the same or different when n is greater than 1 and is -H, aryl, or -C₁₋₃alkyl unsubstituted or substituted with C₆-C₁₀ aryl;

20 R is -H, methyl or ethyl;

R⁴ is 1) hydrogen or -C₁₋₂₀ alkyl, unsubstituted or substituted with one or more of:

- 25 a) -OH,
b) halo,
c) -C₁₋₈ alkoxy,
d) -C₁₋₆ alkenyl,
e) -CONR⁵R⁵, wherein R⁵ is independently
- 30 i) -H,
ii) -C₁₋₈ alkyl unsubstituted or substituted with one or more of R⁷, aryl or heterocyclic, defined below, the aryl being unsubstituted or substituted with one or more of R⁷ or R⁹,

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- iii) aryl unsubstituted or substituted with one or more of R^7 or R^9 , or
iv) heterocyclic, defined below, unsubstituted or substituted with one or more of R^7 or R^9 ,
5 f) $-\text{COOR}^6$, wherein R^6 is
i) $-\text{H}$,
ii) $-\text{C}_{1-8}$ alkyl unsubstituted or substituted with one or more of R^7 or aryl, the aryl being unsubstituted or substituted with one or
10 more of R^7 or R^9 , or
iii) aryl, unsubstituted or substituted with one or more of R^7 or R^9 ,
g) $-\text{S}(\text{O})_p-\text{R}^5$, wherein p is defined above,
h) $-\text{N}(\text{R}^5)_2$,
15 i) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9 ,
j) heterocyclic, unsubstituted or substituted with one or more of R^7 or R^9 ,
k) $-\text{C}_{3-10}$ cycloalkyl, unsubstituted or substituted with
20 one or more of R^7 or R^9 , or
l) $-\text{CONR}^8-\text{CO}-\text{NHR}^8$, wherein R^8 is $-\text{H}$, $-\text{C}_{1-8}$ alkyl, benzyl or cyclohexyl; or
2) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9 , or
25 3) heterocycle or $-\text{C}_{3-10}$ cycloalkyl, either of which is unsubstituted or substituted with one or more of R^7 or R^9 ;
30 R^7 is 1) $-\text{OH}$,
2) $-\text{C}_{1-3}$ alkoxy,
3) $-\text{CN}$,
4) $-\text{COOR}^6$
5) $-\text{C}_{1-8}$ alkyl- COOR^6
6) $-\text{NO}_2$, or

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7) -halo; and

8) amino, mono C₁-C₄ alkylamino, di C₁-C₄ alkylamino;

- 5 R⁹ is 1) -C₁₋₈ alkyl, unsubstituted or substituted with one or more
of aryl or R⁷,
2) -CO-A, -C₁₋₈ alkyl-CO-A, -NHCO-A, or -S(O)_p-A,
wherein p is defined above and A is
a) -H,
10 b) -C₁₋₈ alkyl, unsubstituted or substituted with one or
more of
i) -R⁷, or
ii) aryl, unsubstituted or substituted with one or
more of R⁷, or
15 c) aryl, unsubstituted or substituted with one or more
of R⁷,
3) -NHCO-heterocyclic,
4) -N(R¹⁰)₂ or -CON(R¹⁰)₂ wherein R¹⁰ is independently
-H, heterocyclic, or -A,
20 5) -NHCO-(CH₂)_q-CO-Q, wherein q is 1-4, and Q is
-N(R¹⁰)₂ or -OR¹⁰;

(III A), where:

- 25 A is $(\text{CHR}^1)_n\text{-X-C-R}^4$;
R¹ can be the same or different when n is greater than 1 and is -H,
aryl, or -C₁₋₃alkyl unsubstituted or substituted with aryl;
R is -H, methyl or ethyl;
n is zero through 10;
30 X is -O- or -S-; and
R⁴ is 1) hydrogen or -C₁₋₂₀ alkyl, unsubstituted or substituted with
one or more of:
a) -OH,
b) halo,
c) -C₁₋₈ alkoxy,

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- d) $-C_{1-6}$ alkenyl,
- e) $-\text{CONR}^5\text{R}^5$, wherein R^5 is independently
- 5 i) $-\text{H}$,
 ii) $-C_{1-8}$ alkyl unsubstituted or substituted with
 one or more of R^7 , aryl or heterocycle, the
 aryl being unsubstituted or substituted with
 one or more of R^7 or R^9 ,
- iii) aryl unsubstituted or substituted with one or
10 more of R^7 or R^9 , or
 iv) heterocyclic, unsubstituted or substituted with
 one or more of R^7 or R^9 ,
- f) $-\text{COOR}^6$, wherein R^6 is
- i) $-\text{H}$,
- 15 ii) $-C_{1-8}$ alkyl unsubstituted or substituted with
 one or more of R^7 or aryl, the aryl being
 unsubstituted or substituted with one or
 more of R^7 or R^9 , or
- iii) aryl, unsubstituted or substituted with one or
20 more of R^7 or R^9 ,
- g) $-\text{S(O)}_p-\text{R}^5$, wherein p is zero, 1 or 2;
- h) $-\text{N(R}^5)_2$,
- i) aryl, unsubstituted or substituted with one or more of
 aryl, R^7 or R^9 ,
- 25 j) heterocycle, unsubstituted or substituted with one or
 more of R^7 or R^9 ,
- k) $-C_{3-10}$ cycloalkyl, such as cyclohexyl, norbornyl, or
 adamantyl, unsubstituted or substituted with one
 or more of R^7 or R^9 , or
- 30 l) $-\text{CONR}^8-\text{CO}-\text{NHR}^8$, wherein R^8 is $-\text{H}$, $-C_{1-8}$ alkyl, benzyl
 or cyclohexyl,
 2) aryl, unsubstituted or substituted with one or more of aryl,
 R^7 or R^9 , -

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3) heterocycle or $-C_{3-10}$ cycloalkyl, either of which is
unsubstituted or substituted with one or more of R^7 or
 R^9 ,

4) $-NR^5R^5$, or

5) $-OR^5$;

R^7 is 1) $-OH$,

2) $-C_{1-3}$ alkoxy,

3) $-CN$,

4) $-COOR^6$

5) $-C_{1-8}$ alkyl- $COOR^6$

6) $-NO_2$, or

7) halo; and

8) amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino;

R^9 is 1) $-C_{1-8}$ alkyl, unsubstituted or substituted with one or more
of aryl or R^7 ,

2) $-CO-A$, $-C_{1-8}$ alkyl- $CO-A$, $-NHCO-A$, or $-S(O)_p-A$,

wherein p is defined above and A is

a) $-H$,

b) $-C_{1-8}$ alkyl, unsubstituted or substituted with one or
more of

i) $-R^7$, or

ii) aryl, unsubstituted or substituted with one or
more of R^7 , or

c) aryl, unsubstituted or substituted with one or more
of R^7 ,

3) $-NHCO$ -heterocycle,

4) $-N(R^{10})_2$ or $-CON(R^{10})_2$ wherein R^{10} is independently,
heterocycle or $-A$,

5) $-NHCO-(CH_2)_q-CO-Q$, wherein q is 1-4, and Q is
 $-N(R^{10})_2$ or $-OR^{10}$;

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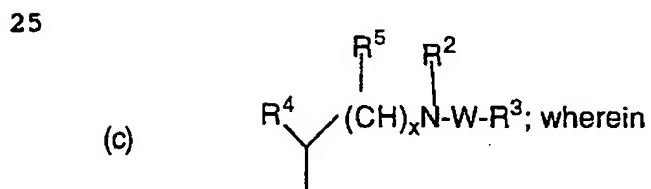
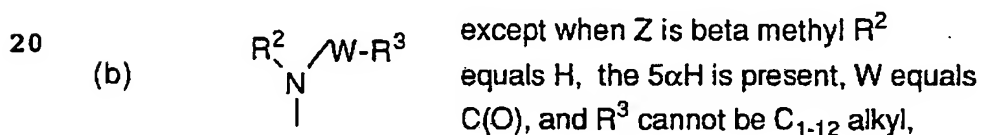
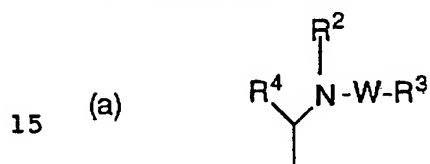
with the provisos that when Z is beta-methyl, the following are excluded:

when n is 1-12, R¹ is -H at each occurrence, X is -O-, and R⁴ is -C₁₋₆alkyl, R⁴ is not substituted with an unsubstituted phenyl ring;

when n is 1-12, R¹ is -H at each occurrence, and X is -O-, R⁴ is not unsubstituted C₅₋₁₀cycloalkyl, unsubstituted phenyl, amino, -C₁₋₈alkyl substituted amino, or -C₁₋₈alkoxy; and

when n is zero, R⁴ is not -CH₃; and

(IVA), where A is:



R² is:
H, methyl or ethyl;

R³ is:
H,
mono C₁-C₄ alkylaminoaryl,

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di C₁-C₄ alkylaminoaryl,
 C₁-20 alkyl,
 C₆-C₁₄ aryl,
 5 heteroaryl, as defined below,
 C₆-C₁₄ arylC₁-20alkyl,
 heteroarylC₁-20alkyl,
 C₁-20alkylthioC₁-20alkyl,
 C₁-20alkylsulfinylC₁-20alkyl,
 C₁-20alkylsulfonylC₁-20alkyl,
 10 C₁-20alkyloxycarbonylC₁-20alkyl,
 carboxylC₁-20alkyl,
 C₁-20 alkylcarbonylC₁-20alkyl,
 C₃-20cycloalkyl,
 C₃-20cycloalkylC₁-20alkyl,
 15 C₆-C₁₄ arylC₁-20alkyloxycarbonylC₁-20alkyl,
 heteroarylC₁-20alkyloxycarbonylC₁-20alkyl,
 haloC₁-20alkyl,
 hydroxylC₁-20alkyl,
 thiosulfatoC₁-20alkyl,
 20 C₆-C₁₄ arylC₁-20alkyloxyC₁-20alkyl,
 C₁-20alkyloxyC₁-20alkyl,
 arylcarbonylarylC₁-20alkyl,
 diarylC₁-20alkyl,
 25 triarylC₁-20alkyl,
 C₂-20 alkenyl,
 C₂-20 alkenylC₁-20alkyl,
 heteroarylC₂-20alkenyl,
 arylC₂-20alkenyl,
 30 C₂-20alkynylC₁-20alkyl,
 arylC₂-20alkynylC₁-20alkyl, or
 heteroarylC₂-20alkynylC₁-20alkyl;

R⁴ is:

H,

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C₁₋₂₀ alkyl,
C₆₋₁₄ aryl or
heteroaryl;

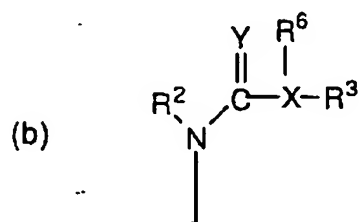
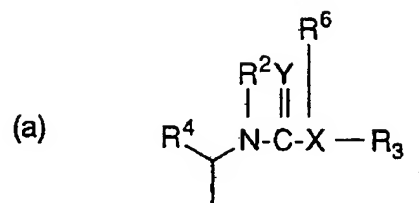
5 R⁵ can be the same or different when X is greater than 1 and is:
H, or
C₁₋₂₀ alkyl;

10 W is:
O
- C -, or
O
- S -,
15 O

x is an integer from 1-25;

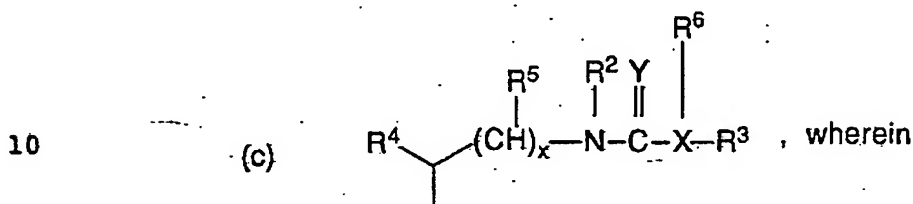
(VA), where:

20 A is:



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except when Z is beta methyl, R² equals H, Y equals O, X equals N and the 5 α H is present, R⁶ and R³ can not be independently selected from H, C₁₋₈ alkyl, C₃₋₆ cycloalkyl, phenyl and R⁶ and R³ cannot
 5 be taken together with the adjacent N to form a 5-6 membered ring comprising up to one other heteroatom selected from O or N, or

R² is:

15 H, or
 C₁₋₂₀ alkyl;

R³ is:

20 H,
 amino,
 mono C₁₋₄ alkylamino,
 di C₁₋₄ alkylamino,
 mono C₁₋₄ alkylaminoaryl,
 di C₁₋₄ alkylaminoaryl,
 C₁₋₂₀ alkyl,
 25 C₆₋₁₄ aryl,
 heteroaryl,
 C₆₋₁₄ arylC₀₋₂₀alkyl,
 C₃₋₂₀ cycloalkyl,
 C₃₋₂₀ cycloalkylC₁₋₂₀alkyl,
 heteroarylC₁₋₂₀alkyl,
 30 C₂₋₂₀ alkenylC₁₋₂₀alkyl,
 haloC₁₋₂₀alkyl,
 C₁₋₂₀alkyloxycarbonyl,
 C₁₋₂₀alkyl,
 C₁₋₂₀ alkyloxyC₁₋₂₀alkyl,

- 15 -

carboxyC₁₋₂₀alkyl,
 C_{6-C14}arylcarbonylarylC₁₋₂₀alkyl,
 C₁₋₂₀alkylcarbonylC₁₋₂₀alkyl,
 C_{6-C14}arylC₁₋₂₀alkyloxy carbonylC₁₋₂₀alkyl,
 5 heteroarylC₁₋₂₀alkyloxy carbonylC₁₋₂₀alkyl,
 hydroxylC₁₋₂₀alkyl,
 halohydroxylC₁₋₂₀alkyl,
 arylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
 heteroarylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
 10 diarylC₁₋₂₀alkyl,
 triarylC₁₋₂₀alkyl,
 C₂₋₂₀alkenyl,
 C₂₋₂₀alkenylC₁₋₂₀alkyl,
 C₂₋₂₀alkynylC₁₋₂₀alkyl,
 15 arylC₂₋₂₀alkynylC₁₋₂₀alkyl,
 heteroarylC₂₋₂₀alkynylC₁₋₂₀alkyl,
 C₁₋₂₀alkylthioC₁₋₂₀alkyl,
 C₁₋₂₀alkylsulfonylC₁₋₂₀alkyl, or
 20 C₁₋₂₀alkylsulfinyl C₁₋₂₀alkyl;

R⁴ is:

H,
 C₁₋₂₀alkyl,
 25 heteroaryl, or
 C_{6-C14}aryl;

R⁵ can be the same or different when X is greater than 1 and is:

H,
 30 C₁₋₂₀alkyl,
 heteroaryl, or
 C_{6-C14}aryl;

R⁶ is present when X equals N and is independently

H,

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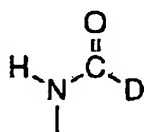
or C₁-C₂₀ alkyl and can be taken together with R³ and the N to which they are attached to form a heteroaryl ring system; as defined below, and

5

(VIA), where:

A is (a)

10



D is R¹ or OR¹,

where R¹ is: C₁-C₁₀alkyl,

C₃-C₁₂cycloalkyl,

15

C₆-C₁₀aryl, or

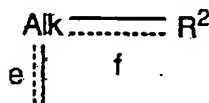
C₇-C₁₁aralkyl with the proviso that when D is R¹ and Z is beta-methyl, the value of C₁-C₁₀ alkyl is excluded; and

20

(b) $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{OC}_1-\text{C}_{12} \text{ alkyl} \end{array}$, providing Z is not methyl;

(VIA), where A is of the formula:

25



wherein:

Alk is C₁-C₄ straight or branched chain alkyl or alkenyl; dashed lines e and f each can independently represent a double bond when present, with the proviso that double bonds formed by e and f are not both present concurrently; and

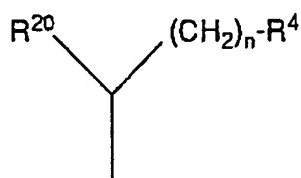
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R² is (a) C₆-C₁₀ aryl, or 5-6 membered heteroaryl radical which can contain 1-4 nitrogen atoms, one oxygen or sulfur atoms or combinations thereof with 1-2 nitrogen atoms;

- 17 -

- (b) COR_1 , where R_1 is C_6 - C_{10} aryl, substituted C_6 - C_{10} aryl, and heteroaryl;
 (c) CONHR_2 , where R_2 is substituted phenyl, heteroaryl, substituted heteroaryl, or C_7 to C_{12} cycloalkyl;
 5 (d) CO_2R_3 , where R_3 is C_1 - C_{18} linear or branched alkyl, C_6 - C_{10} aryl, substituted C_6 - C_{10} aryl, or C_7 - C_{12} cycloalkyl; providing that in (b), (c) or (d), Alk is only alkenyl;

10 (VIII A), where A is of the structure:



15 where:

R^{20} is H, methyl;

n is 0-10

20 R^4 is selected from:

- (a) $-\text{COR}^1$, where R^1 is phenyl or substituted phenyl;
 (b) $-\text{CONHR}^2$, where R^2 is substituted phenyl, heteroaryl, substituted heteroaryl;
 (c) $-\text{COOR}^3$, where R^3 is phenyl, substituted phenyl, heteroaryl, substituted heteroaryl; wherein said heteroaryl radical is a 5-6 membered ring which can contain 1-4 nitrogen atoms, one oxygen or sulfur atom, or combinations thereof with 1-2 nitrogen atoms, and wherein phenyl and heteroaryl can be substituted; wherein the above aryl or heteroaryl radicals can also be fused with a benzo or another heteroaryl ring and can further be substituted with one or more substituents; and stereoisomers and

- 18 -

pharmaceutically acceptable salts and esters thereof.

5 Also disclosed are processes for their preparation, pharmaceutical formulations comprising the novel compounds as active ingredients and methods of inhibiting prostatic and scalp 5 α -reductases in diseases which occur under hyperandrogenic conditions, e.g. benign prostatic hyperplasia, with the novel compounds and their pharmaceutical formulations.

10

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

15 The description of the novel 7-substituted compounds disclosed and encompassed by this invention is conveniently discussed in terms of the 17-A substituent categories IA-VIIIA. It is to be noted that there may be some duplication of symbols of radicals which have slightly different meanings, e.g., where A is IA, the R³ radical represents H, methyl or ethyl; however, where A is IVA, R³ represents a long list of possible radicals. However, within a given
20 17-A substituent category, the nomenclature is consistent. Therefore, the discussion of the synthesis, properties and description of the compounds herein must first refer to the specific 17-A structure IA-VIIIA being discussed.

25 The following is a detailed description of the 7-position radical Z as used herein.

By the term "C₁-C₄ alkyl" as used herein, is meant to include: e.g. methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl and t-butyl.

30 By the term "C₂-C₄ alkenyl" as used herein is meant to include: vinyl, allyl, 1-propen-1-yl, 1-propen-2-yl, 1-buten-1-yl, 1-buten-2-yl, and the like.

By the term "C₃-C₆ cycloalkyl" as used herein is meant to include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

- 19 -

By the term "halo" as used herein is meant to include: fluoro, chloro, bromo, iodo.

By the term " $\text{OC}_1\text{-C}_4$ alkyl" as used herein is meant to include: methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy.

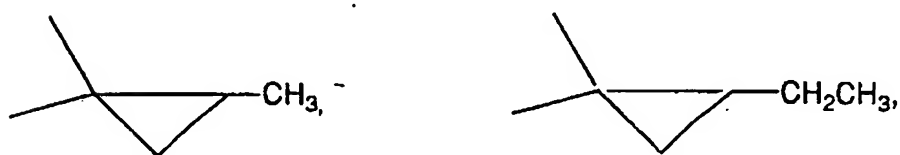
By the term " $\text{OC}_3\text{-C}_6$ cycloalkyl" as used herein is meant to include: cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy.

Representative examples of Z are where α -substituent (dashed lines) is hydrogen and the beta substituent (wedge) is e.g. methyl, ethyl, propyl, allyl, carboxymethyl, hydroxy, methoxy, ethoxy, cyclopropyloxy, cyclopentyloxy, acetoxy, fluoro, chloro, bromo, trifluoromethyl, trichloromethyl, fluoromethyl, chloromethyl, carboxy, N,N-dimethylcarbamoyl, hydroxymethyl, methoxymethyl, and the like.

Representative examples where Z is an alkenyl substituent, $=\text{CH-R}'$, includes, e.g. $=\text{CH}_2$, $=\text{CH-CH}_3$, $=\text{CH-CH}_2\text{CH}_3$, and the like.

Representative examples where R^1 , R^2 and the N can form a heterocyclic ring include: N-morpholinyl, N-(4-methyl)piperazinyl, N-piperidinyl, and the like.

Representative examples where Z is the spiro substituent:



- 20 -

stereoisomers thereof and the like.

Unless otherwise indicated the 17-position substituent is assumed to be in the beta configuration.

5

Representative compounds included in the invention wherein all of the 7- and 17-substituents are in the beta configuration are:

10

4,7 β -Dimethyl-4-aza-Androst-5-en-3-one-17 β -ol, t-butyl dimethylsilyl ether,

4,7 β -Dimethyl-4-aza-Androst-5-en-3-one-17 β -ol,

15

4,7 β -Dimethyl-4-aza-androstan-3-one-17 β -ol,

17 β -Pivaloyloxy-4,7 β -Dimethyl-4-Aza-Androstan-3-one,

20

17 β -(t-Butylaminocarbonyloxy)-4,7 β -dimethyl-5 α -4-Aza-Androstan-3-one,

17 β -Methoxycarbonyl-4-methyl-4-aza-androst-5-en-3,7-dione,

25

17 β -t-Butylcarbonylamino-4,7 β -dimethyl-4-aza-5 α -androstan-3-one,

30

17 β -(1-Adamantylloxy)carbonylamino-4,7 β -dimethyl-4-aza-5 α -androstan-3-one,

17 β -Benzoylamino-4,7 β -dimethyl-4-aza-5 α -androstan-3-one,

17-Oximino-4,7 β -Dimethyl-4-aza-5 α -androstan-3-one,

- 21 -

7 β -Acetoxy-17 β -carbomethoxy-4-methyl-4-aza-5 α -androstan-3-one,

5 17 β -(1-adamantyl)carbonylamino-4,7 β -dimethyl-4-aza-5 α -androstane-3-one,

4,7 β -dimethyl-4-aza-5 α -androstan-3,17-dione,

10 17 β (N,N-diisopropyl)carboxamido-4-methyl-4-aza-5 α -androstan-3,7-dione

17 β -Benzylcarbonylamino-4,7 β -dimethyl-4-aza-5 α -androstan-3-one.

15 The first group of preferred compounds of this invention can be made by procedures outlined in the following Flowsheets:

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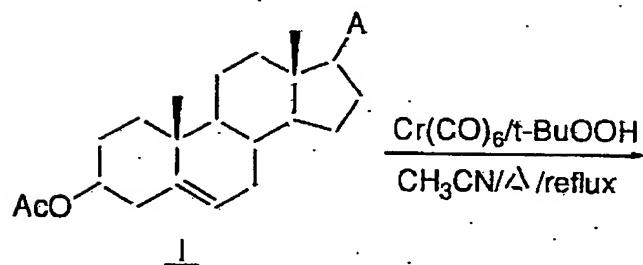
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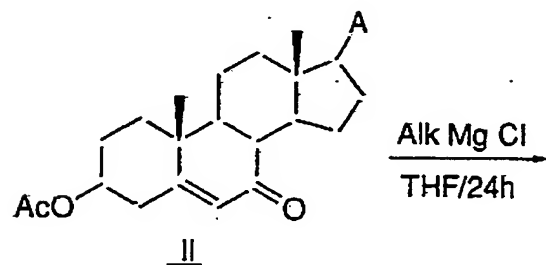
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GENERAL FLOWSHEET I

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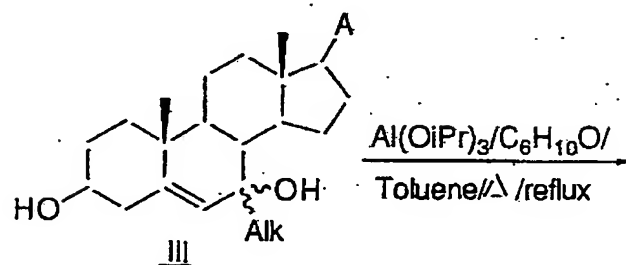


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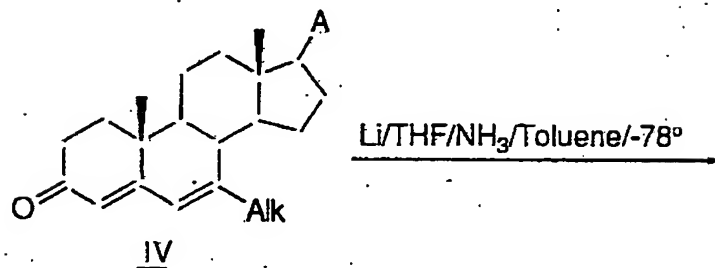
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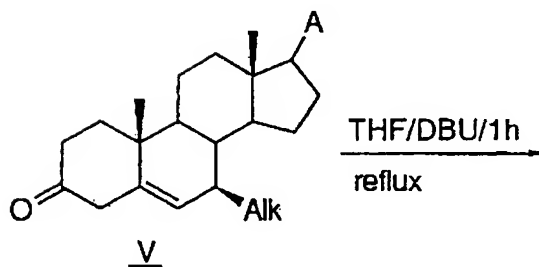
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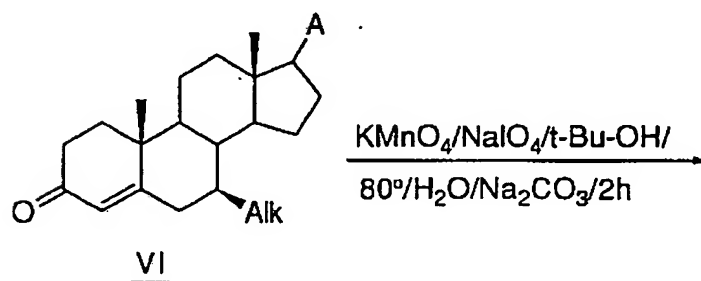
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GENERAL FLOWSHEET I (CONT'D)

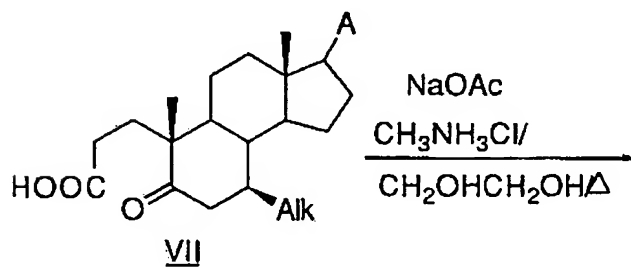
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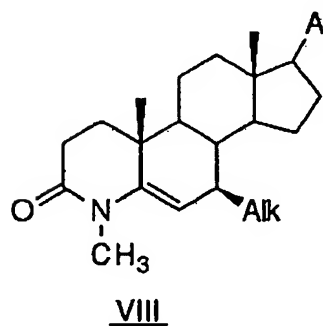
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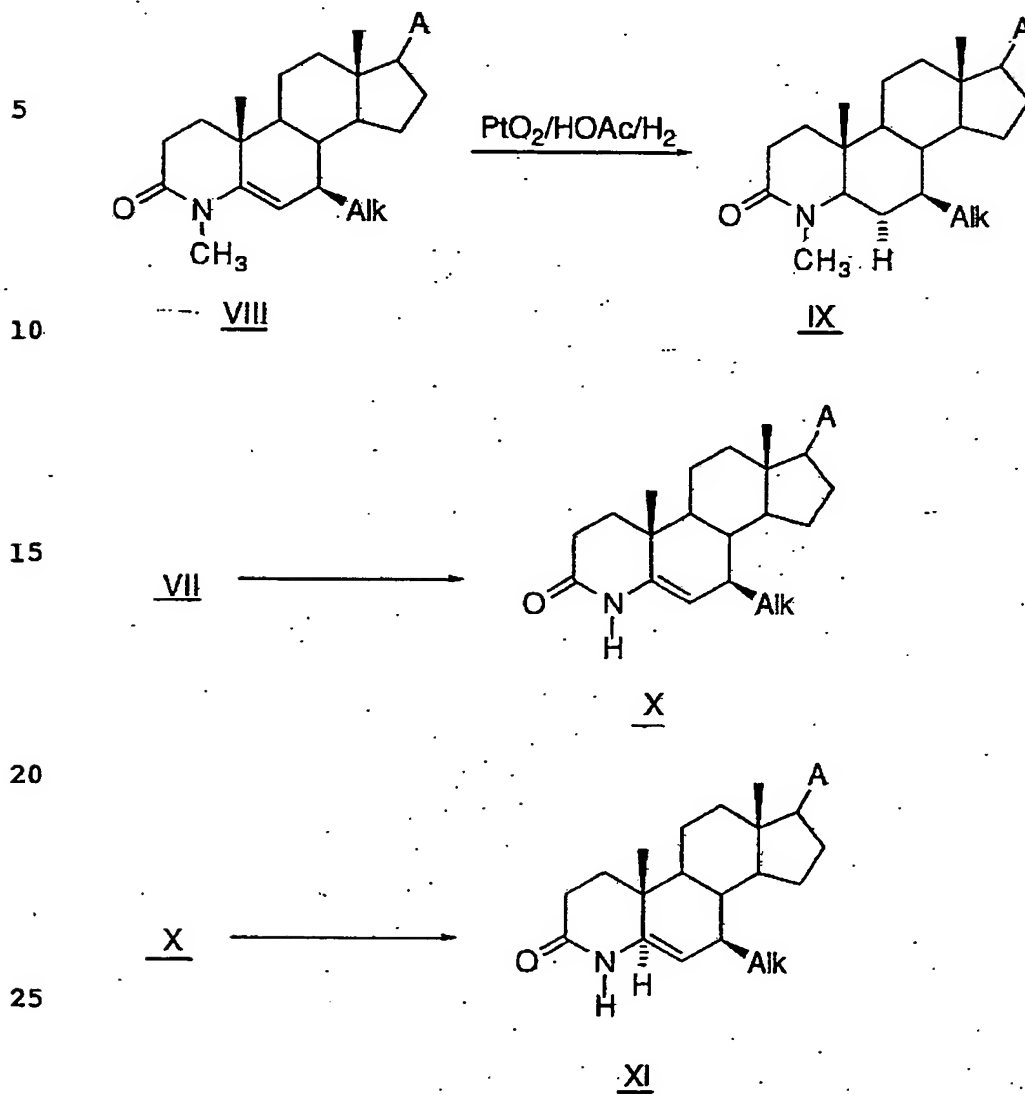
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GENERAL FLOWSHEET I (CONT'D)



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- 26 -

7-Beta Alkyl-17-A Series

The compounds of the instant invention comprising Z as a 7 β alkyl group, e.g. methyl, ethyl, isopropyl, where A is defined above, can be prepared by the procedure outlined in The General
5 Flowsheet.

As seen in the Flowsheet, the 3-acetoxy-androst-5-en-17-A I is oxidized to the corresponding 5-en-7-one II by treatment with hydrogen t-butyl peroxide and chromium hexacarbonyl in e.g. acetonitrile, at reflux. The C₁-C₄ alkyl group, designated Alk, e.g.
10 methyl, can be introduced at this point by a Grignard reaction using e.g., alkyl magnesium chloride in e.g., anhydrous THF at 0-10°C to produce the 7-alkyl-7-hydroxy adduct III. This is then oxidized with e.g. aluminum isopropoxide and cyclohexanone (Oppenauer oxidation conditions) in refluxing toluene solvent to produce the 7-
15 alkyl-4,6-dien-3-one IV. This in turn is reduced via a e.g., metal-ammonia reduction, using e.g., lithium, liquid ammonia, THF and toluene at -78°C to selectively yield the 7-beta-alkyl-5-en-3-one V. In the next step the delta-5 double bond is isomerized to the 4-ene by use of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in, e.g. refluxing
20 tetrahydrofuran (THF) to produce the 7-alkyl 4-en-3-one, VI. The A Ring is next cleaved by treatment with e.g. potassium permanganate, sodium periodate in t-butyl alcohol at 80°C to produce the corresponding seco-acid VII. Treatment of the seco-acid with an appropriate amine e.g., methylamine hydrochloride and
25 sodium acetate in ethylene glycol at 180°C, yields e.g., the 4-methyl-4-aza-androst-5-en-3-one VIII. This in turn is selectively reduced with e.g., PtO₂, to remove the 5- double bond to produce the 5 α -hydrogen compound IX. The seco-acid VII can be similarly treated with ammonia to produce the corresponding N-H compound, X,
30 which can then be analogously treated with PtO₂ to produce the corresponding 5 α -4N-H compound XI.

Throughout this series of reactions, the 17-A group should be inert to the individual reaction conditions and can be practiced with all of the herein disclosed 17-A side chains. There is

- 27 -

now presented a sub-series of flowsheets denoted letter A through letter I.

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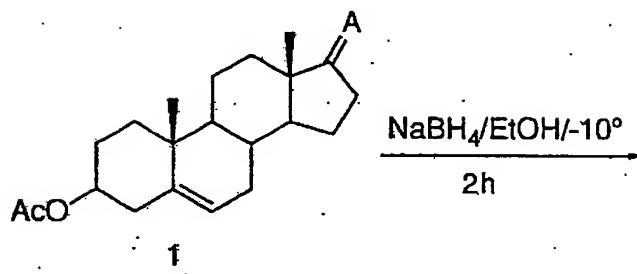
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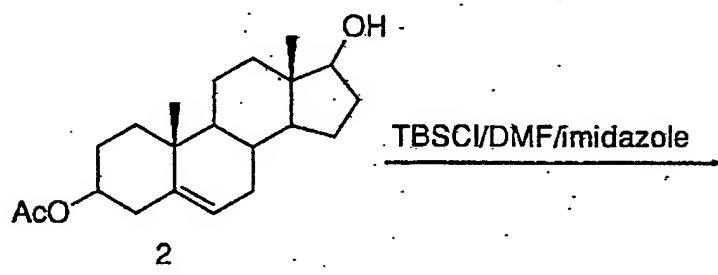
- 28 -

FLOWSHEET A

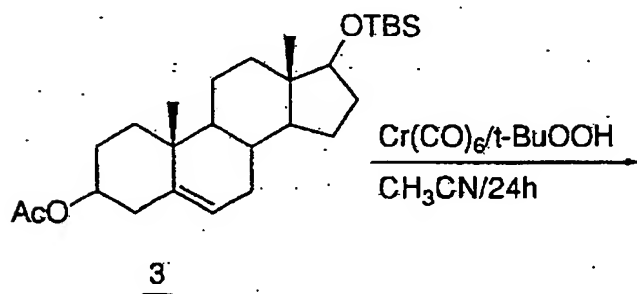
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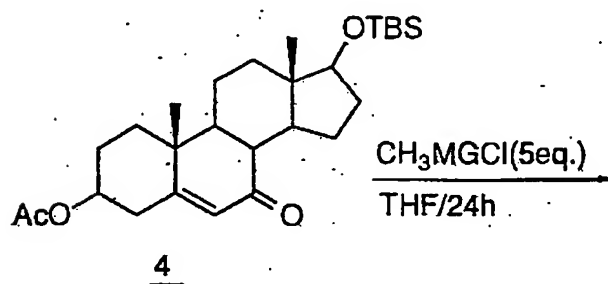


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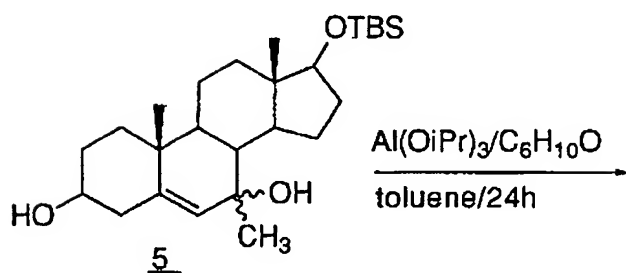


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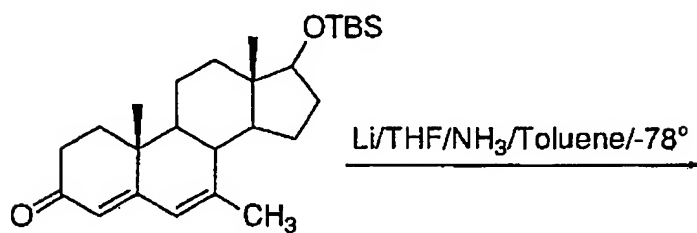
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FLWSHEET A (CONT'D)

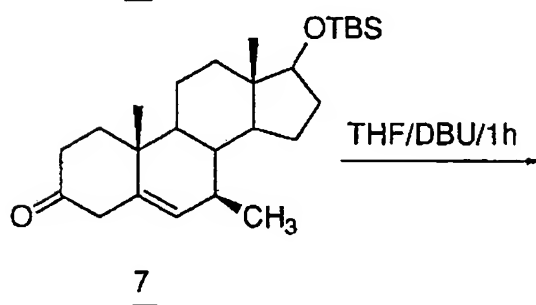
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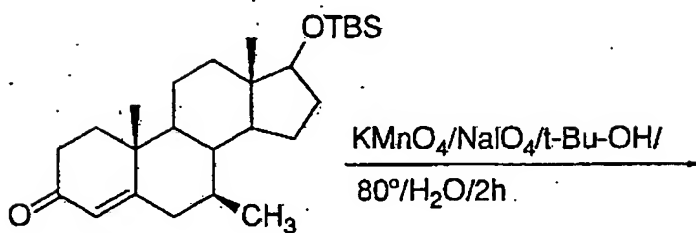
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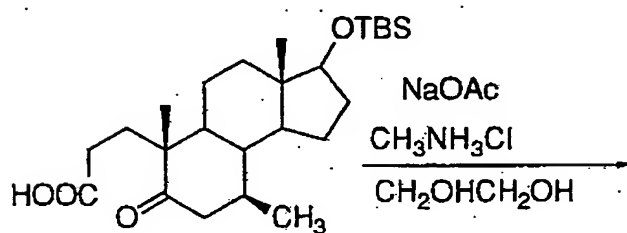
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FLWSHEET A (CONT'D)

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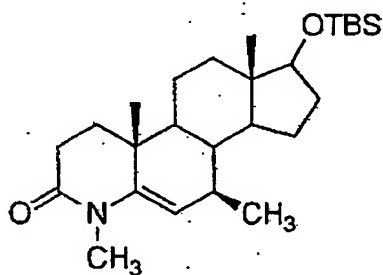
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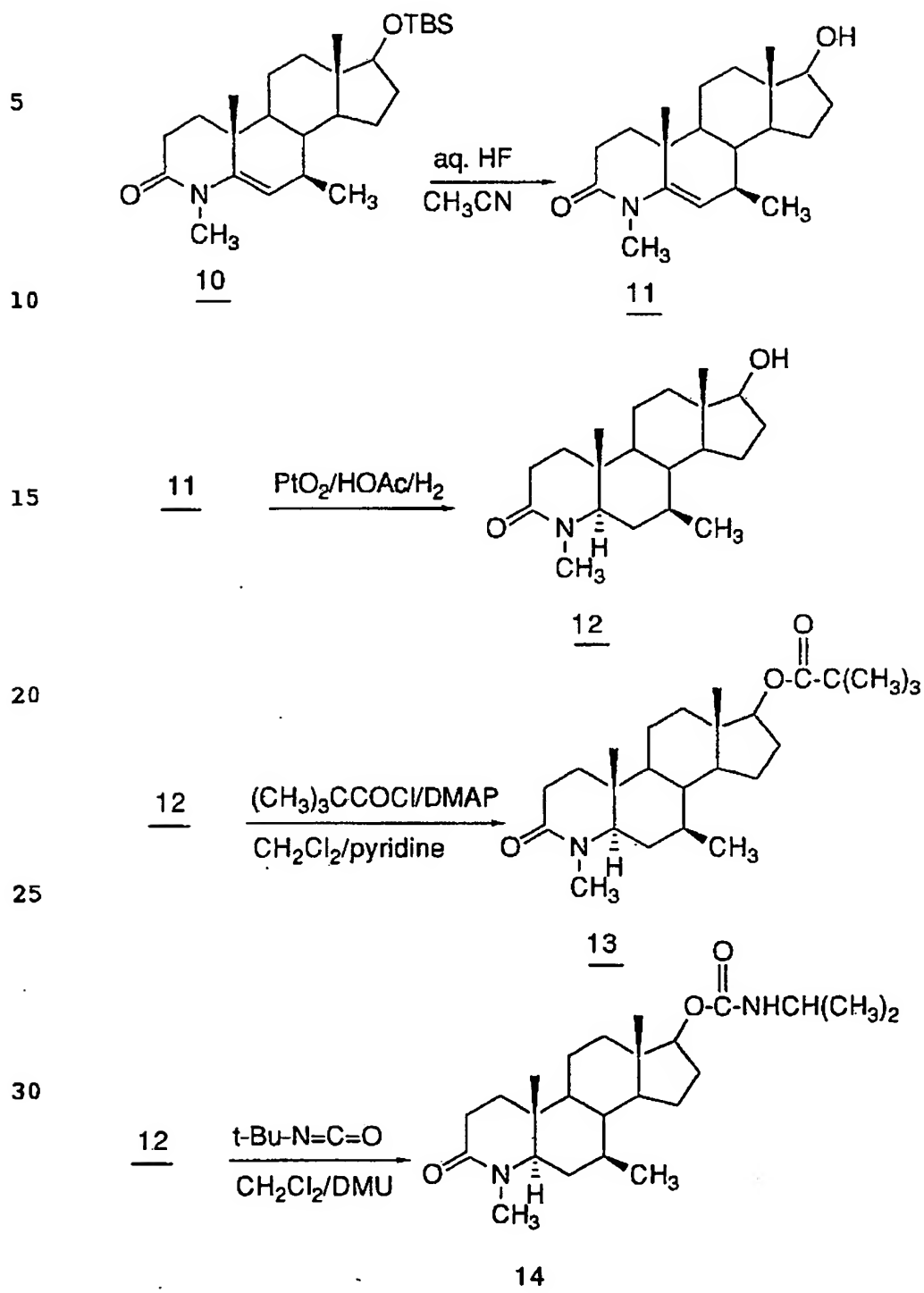
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FLOWSHEET B



7-Beta Alkyl-17-Oxy-Androstanes

The compounds of the instant invention where A is hydroxy or derivatived hydroxy and Z is an 7 β alkyl group, e.g. methyl, ethyl, propyl, isopropyl, allyl, can be prepared by the procedure outlined in Flowsheets A and B.

As seen in Flowsheet A, the 3-acetoxy-androst-5-en-17-one 1 is reacted with sodium borohydride in a suitable solvent, e.g. ethanol, at -10°C to stereospecifically reduce the 17-ketone to the 17 β -ol 2. The 17-hydroxy group is protected with the TBS group (t-butyldimethyl-silyl) by reacting TBS chloride with 2 in a suitable solvent, e.g. DMF in the presence of the proton acceptor, e.g. imidazole, at room temperature, to form 3.

Following the hydroxy protection, this compound is oxidized in the seven position to the corresponding 5-en-7-one 4 by treatment of 3 with hydrogen t-butyl peroxide and chromium hexacarbonyl in e.g. acetonitrile, at reflux. The alkyl group, e.g. methyl, can be introduced at this point by a Grignard reaction using e.g., methyl magnesium chloride in anhydrous THF at 0-10°C to produce the 7-methyl-7-hydroxy adduct 5. This Grignard product is then oxidized with aluminum isopropoxide and cyclohexanone (Oppenauer oxidation conditions) in refluxing toluene solvent to produce the 7-methyl-4,6-dien-3-one 6. This in turn is reduced via a metal-ammonia reduction using lithium in liquid ammonia, THF and toluene at -78°C to selectively yield the 7-beta-methyl-5-en-3-one 7. In the next step the 5-double bond is isomerized to the 4-ene by use of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in refluxing tetrahydrofuran (THF) to produce the 4-en-3-one, 8. The A Ring is next cleaved by treatment with potassium permanganate, sodium periodate in t-butyl alcohol at 80°C to produce the corresponding seco-acid 9. Treatment of the seco-acid 9 with an appropriate amine, e.g., methylamine hydrochloride and sodium acetate in ethylene glycol at 180°C, yields the 4-aza-androst-5-en-3-one 10. The TBS protecting group is then removed e.g., by aqueous HF in acetonitrile

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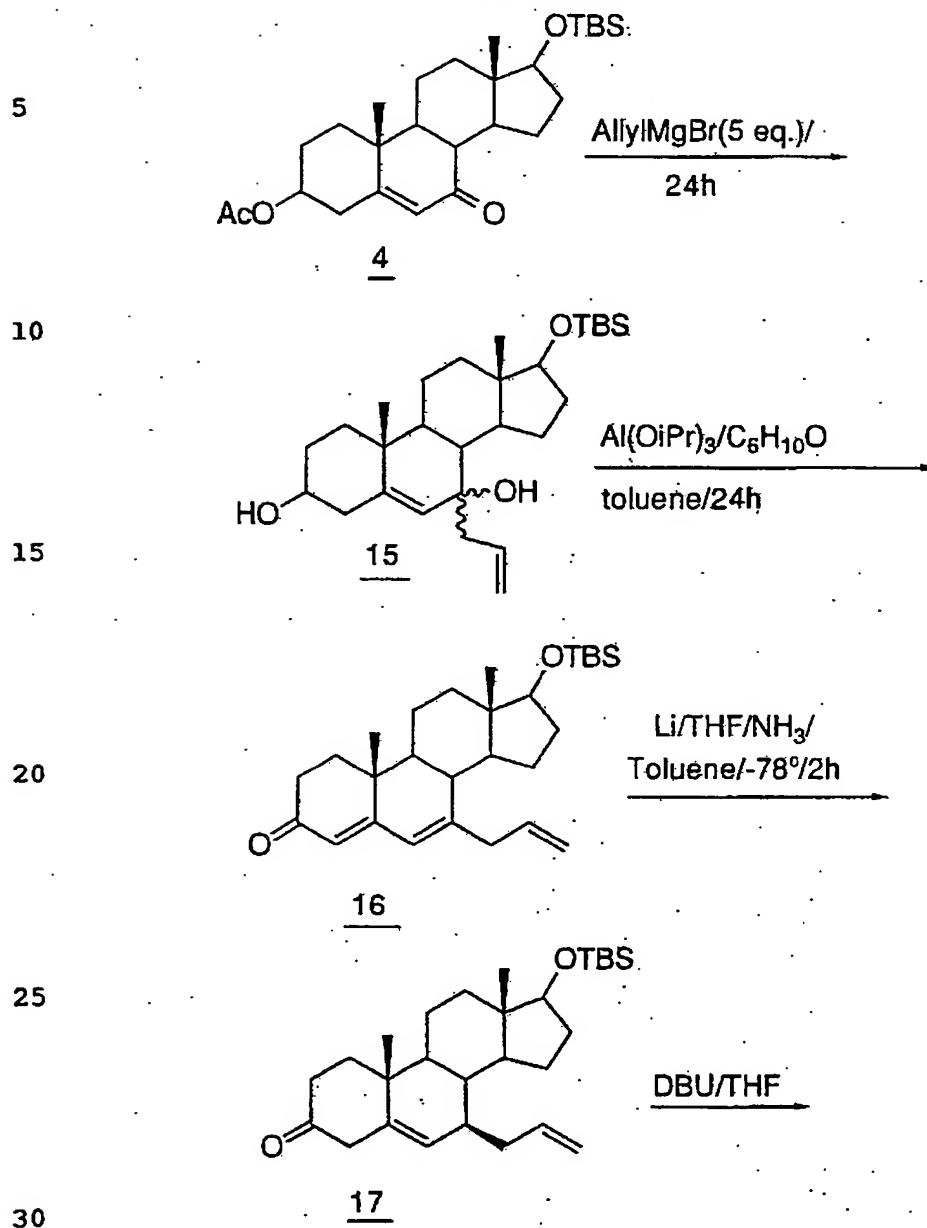
at 0°C, to yield the 17- β alcohol 11. This in turn is selectively reduced to remove the 5-double bond to produce the 5 α -hydrogen compound 12. At this point, the 17 β hydroxy group can be derivatized with a variety of reagents. For example, it can be esterified with an acid moiety, e.g. t-butyl acid chloride in a solvent, e.g., pyridine, to produce the t-pentanoic acid ester 13.

Further, 12 can be reacted with an isocyanate, e.g. t-butyl-isocyanate in a solvent and in the presence of DBU to yield the urethane ester 14.

Similarly, other acylating agents obvious to one skilled in the art can be used to derivatize the 17-beta-ol grouping.

Carrying out the above series of reactions but using, e.g. ethyl magnesium chloride as the Grignard reagent, leads to the corresponding 7-beta ethyl analogs.

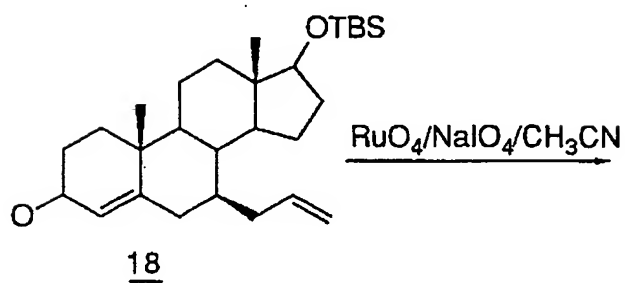
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FLWSHEET C

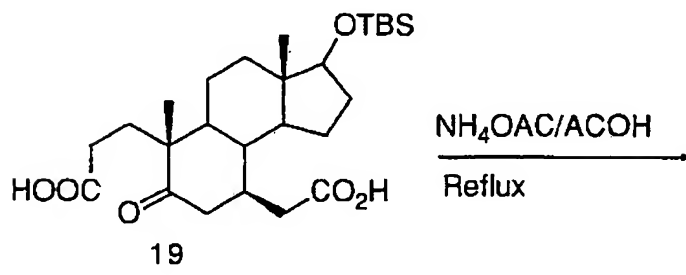
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FLWSHEET C (CONT'D)

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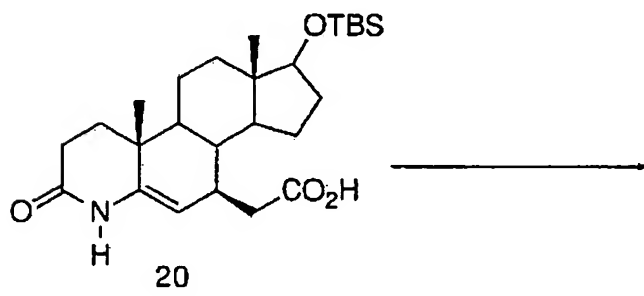


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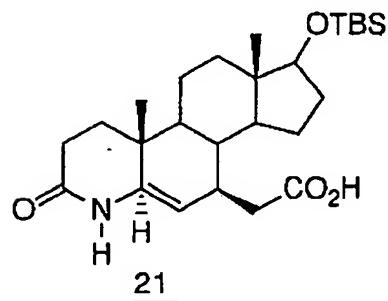
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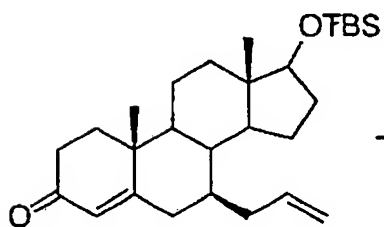
7-Carboxymethyl-17-OTBS Series

The 7-carboxy substituent is formed through the corresponding 7-allyl group. As seen in Flowsheet C, acetate 4 is reacted with allyl Grignard reagent to form the adduct 15 which is oxidized to the dienone 16 by Oppenauer oxidation conditions. Metal-ammonia reduction affords the 5-ene analog 17, followed by DBU-catalyzed double bond isomerization to 18. This in turn is oxidized in a key step with potassium permanganate, sodium periodate in t-butanol to form the 7-carboxymethyl seco-acid 19. Treatment with amines, e.g. ammonium salts, forms the 4-aza derivative, 20 which is then reduced to the 5- α 21. Use of methylamine in place of ammonia yields the corresponding 4-methyl analogs of 20 and 21.

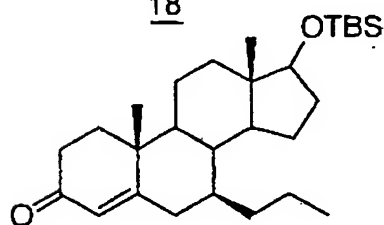
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FLWSHEET D

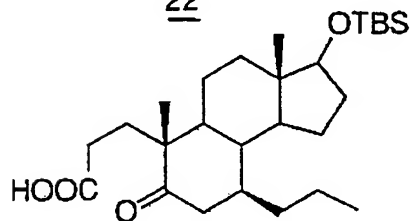
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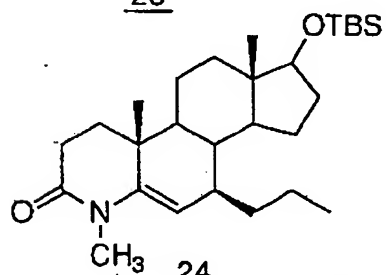
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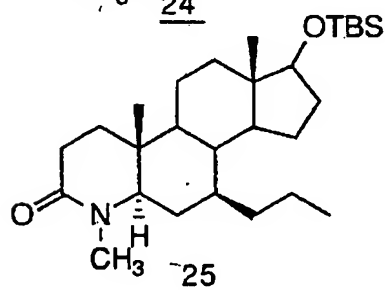
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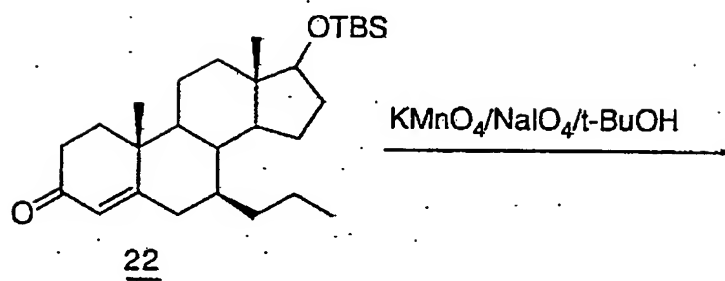
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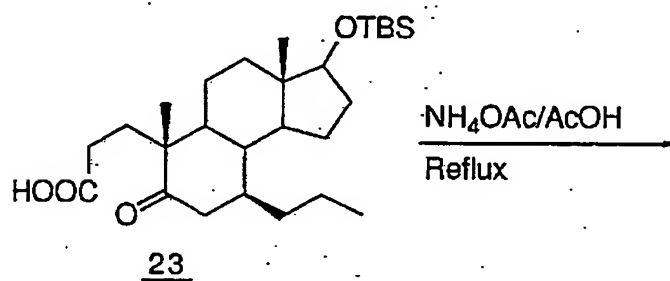
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FLOWSHEET E

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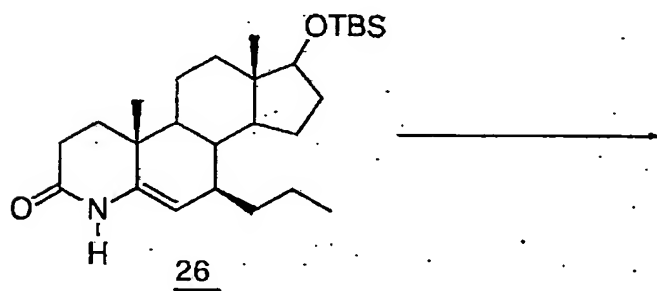


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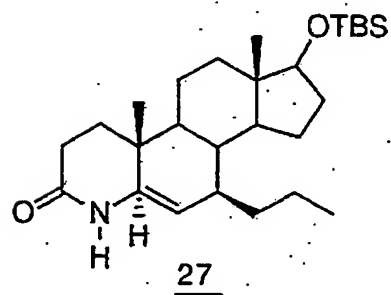


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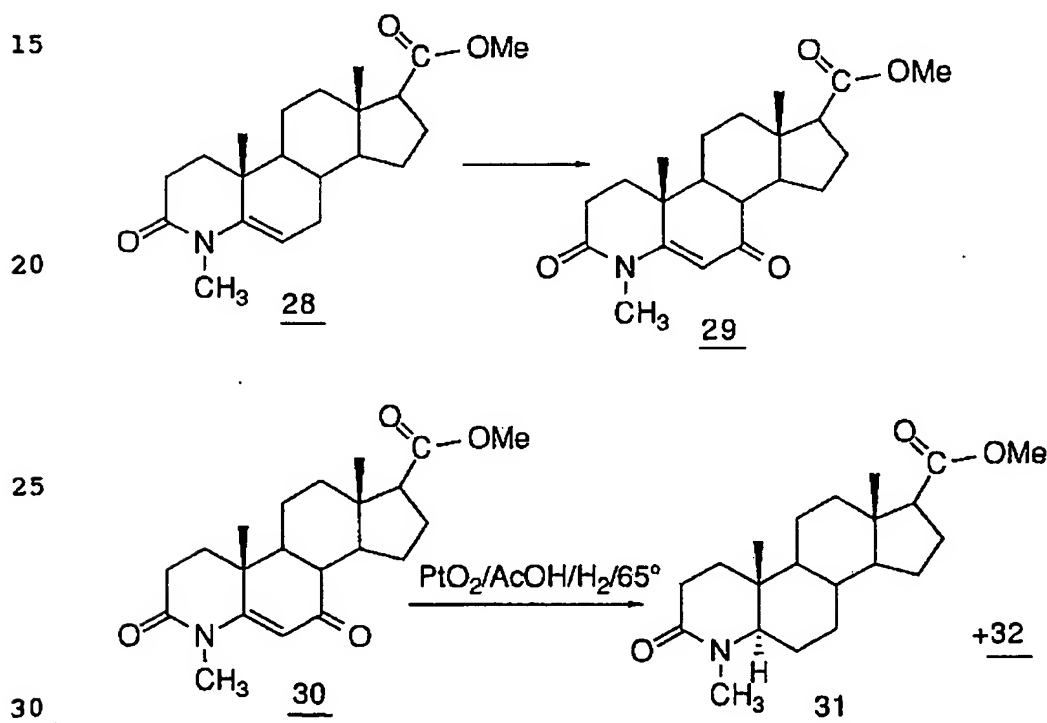


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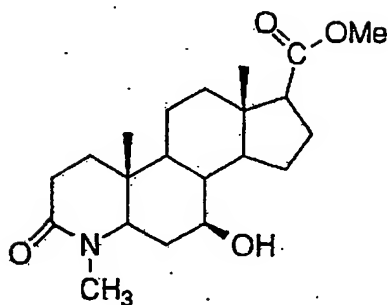
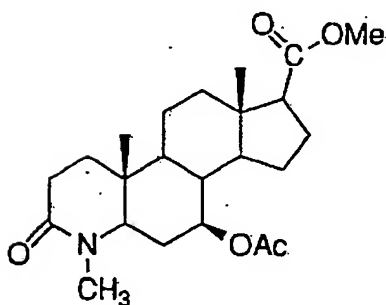
- 39 -

7-Propyl-17-OTBS Series

The 7-propyl analogs are made as illustrated in Flowsheet D starting with the 7-allyl-4-en-3-one 18, which is reduced by Wilkinson's catalyst to the propyl derivative 22, oxidized to the seco-acid 23, then condensed with amines, e.g. methylamine, to form the 4-methyl analog 24 and then reduced to the 5- α 25. Corresponding treatment with ammonia is shown in Flowsheet E shows the corresponding unsubstituted 4-aza 26 and 5- α 27 analogs.

FLWSHEET F

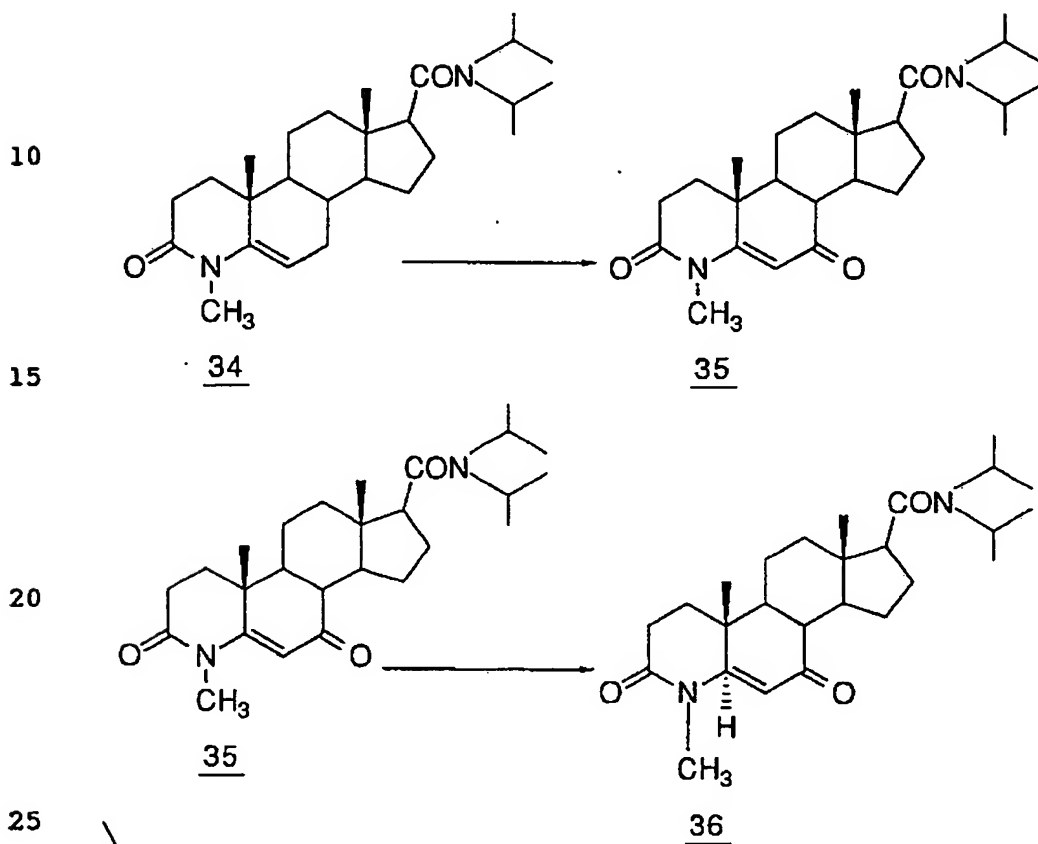
- 40 -

FLWSHEET G32 $\text{AC}_2\text{O/Py/DMAP/CH}_2\text{Cl}_2$ 337-Beta Acetoxy 17-carboxyester Series

The 7-beta acetoxy series is prepared as illustrated in Flowsheets F and G by the oxidation of starting ester 28 to the 5-en-7-one 29 by the chromiumhexacarbonyl/t-butylhydroperoxide/-acetonitrile procedure described above. Platinum catalyzed hydrogenation of 29 yields two products, the fully reduced 7-H

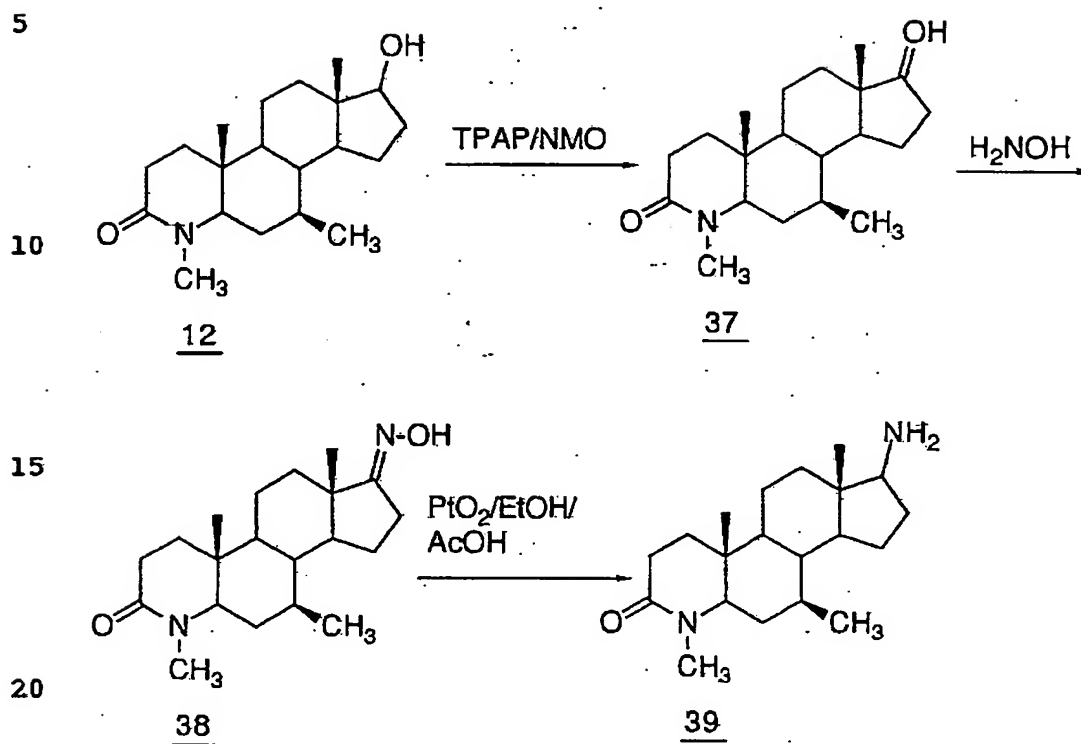
- 41 -

compound 31, and 7-beta hydroxy compound 32. Acylation of 32 with acetic anhydride yields the 7-beta acetoxy compound 33.

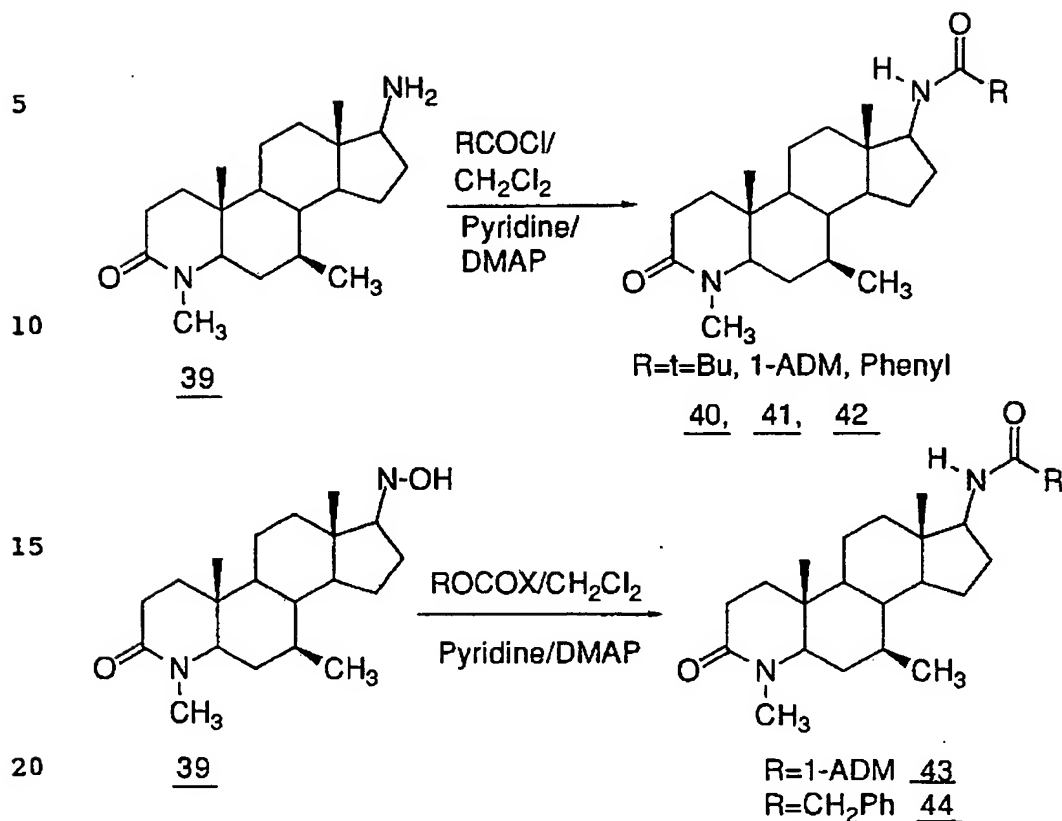
FLWSHEET H7-Keto-17-Carboxamide Series

The compound 34 is known in the art. This in can be
30 oxidized with the chromium carbonyl reagent to yield the 5-en-7-one
35. The 5-double bond is catalytically reduced to yield the 7-one 36.

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FLWSHEET I

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FLWSHEET I (CONT'D)7-Beta Methyl-17-Aza Series

25 This series can be prepared as illustrated in Flowsheet I starting with the 7-beta methyl-4-N-methyl-17-ol 12. This is oxidized to the 17-keto compound 37, by the use of tetrapropylammonium perruthenate (TPAP) and N-methylmorpholine-N-oxide (NMO) at room temperature. This is

30 reacted in turn with hydroxylamine in ethanol, pyridine at 100°C to form the oxime 38, which is catalytically hydrogenated with platinum oxide in ethanol/acetic acid at room temperature to form the 17-amino 39.

The amine 39 can be reacted with a variety of acylating agents. Reaction with pivaloyl chloride in methylene chloride,

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pyridine, 4-dimethylamino pyridine (DMAP), yields 40, the "reverse finasteride"; reaction with 1-adamantane carbonyl chloride yields the 1-ADM 41; and reaction with benzyl chloride yields the benzoyl derivative 42.

Reaction of the amine 39 with different chloroformates yields the corresponding urethanes. Reaction of 39 with 1-adamantyl fluoroformate in DMAP, pyridine and methylene chloride yields the urethane 43; reaction with e.g. benzyl chloroformate correspondingly yields 44.

Other acylating agents and chloroformates known in the art can be used to produce the corresponding acyl and urethane compounds.

The above 7-substituents can be introduced into all of the compounds defined for the 17-A group herein by appropriate analogous procedures.

Accordingly, the present invention is particularly concerned with providing a method of treating the hyperandrogenic conditions of androgenic alopecia, acne vulgaris, seborrhea, and female hirsutism, benign prostatic hyperplasia, prostatitis, the prevention and/or treatment of prostatic carcinoma, by oral, topical, or parenteral administration, of the novel compounds of the present invention.

The following examples are illustrative of representative preferred embodiments of this invention and should not be construed to be limits on the scope or spirit of the instant invention.

EXAMPLES FOR THE CASE WHEN SUBSTITUENT "A" OF
GENERAL FORMULA "I" IS AS DEFINED IN GROUP "VI(A)"

EXAMPLE 1

Synthesis of 3-Acetoxy-Androst-5-en-17-ol (2)

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To a solution of 100 mg. (0.303 mmol) of 3-acetoxy-androst-5-en-17-one, 1, in 3 ml EtOH at -10°C, was added 22.9 mg (0.606 mmol) of sodium borohydride with stirring. After the reaction mixture was stirred for one and 1/2 hours, the mixture was diluted with 10 ml water, the ethanol solvent removed under vacuum, and the residue extracted with ethyl acetate. The organic layer was washed with aqueous Na₂CO₃, brine, dried over sodium sulfate and concentrated to leave a residue of crude title compound 2. Proton NMR confirmed the assigned structure.

EXAMPLE 2

Synthesis of 3-Acetoxy-Androst-5-en-17-ol, 17-t-butyl-dimethylsilyl ether (3)

To a solution of the androstan-17-ol, 2, from Example 1, being 4.5 g (13.55 mmol) in 50 ml. dimethylformamide at 23°C was added 2.76 g (40-65 mmol) imidazole followed by 3.063 g (20.32 mmol) of t-butyldimethylsilyl chloride. The reaction mixture was stirred and a solid began to precipitate. Twenty additional ml of DMF were added and the mixture further stirred overnight. The mixture was poured into 1 liter water, the solid filtered and washed with water. The solid was dissolved in ethylacetate, the organic layer washed with brine and dried over sodium sulfate, concentrated to yield the silyl protected 17-ol title compound 3. The proton NMR confirmed the assigned structure.

EXAMPLE 3

Synthesis of 3-Acetoxy-Androst-5-ene-7-one-17β-ol, 17-t-butyldimethylsilyl ether (4)

To a solution of the TBMS protected 17-ol 3 from Example 2, being 5.6 g (12.55 mmol) in 100 ml acetonitrile at 23°C was added 90% t-butyl hydrogen peroxide, 3.958g (43.92 mol), and 138 mg chromium hexacarbonyl. After refluxing the mixture under

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nitrogen for 24 hours, the reaction mixture was poured into one liter water, solid was filtered, the residue washed with 500 ml water and the residue dissolved in 350 ml methylene chloride. The organic layer was washed with brine, dried over sodium sulfate and concentrated to yield crude material. Thin layer chromatography (3:1 hexane/ethyl acetate on silica gel) showed the presence of starting material. The solid was purified by column chromatography over silica gel by elution with 7% ethyl acetate/hexane to yield the title compound 4. Proton NMR confirmed the assigned structure.

EXAMPLE 4

Synthesis of 3,7-Dihydroxy-7-methyl-Androst-5-en-17B-ol, 17-TBMS ether (5)

To a solution of the product 4 from Example 3, being 440 mg. (0.956 mmol) in dry tetrahydrofuran at 0°C was added dropwise methyl magnesium chloride over 5-10 minutes. The reaction mixture was then allowed to stir at room temperature for 24 hours, then poured into saturated aqueous ammonium chloride. The THF solvent was removed under vacuum and the aqueous phase extracted with ethyl acetate. The organic layer was washed with brine, dried, concentrated to yield crude product. Proton NMR confirmed the assigned structure of the title compound 5 which was used in the next step without further purification.

EXAMPLE 5

Synthesis of 7-methyl-Androst-4,6-dien-3-one-17B-ol, 17-t-butyl(dimethylsilyl) ether (6)

The above Grignard product 5, 3.5g. (7.142 mmol) was dissolved in 50 ml toluene/50 ml. cyclohexanone and 20 ml of solvent distilled off under vacuum. To this was added 4.54 g. aluminum isopropoxide and the reaction mixture refluxed overnight for 15 hours. The mixture was cooled, diluted with ethyl acetate,

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washed with sodium potassium tartarate, brine, and the organic layer was concentrated under vacuum and the residue steam distilled. The residue was extracted with ethyl acetate, washed with brine, dried and purified by column chromatography on silica gel, eluting with 5% EtOAc/hexane to yield the title compound 6.

EXAMPLE 6

Synthesis of 7 β -Methyl-Androst-5-en-3-one-17 β -ol, t-Butyldimethylsilyl ether, (7)

To a solution of 370 mg of 6, from Example 5, in 5.5 ml ammonia, 1 ml THF, 1 ml. toluene, was added 50 mg. of metallic lithium in small pieces. After stirring the blue solution for 2 hours, a solution of 1,2-dibromethane in 2 ml THF was added. After stirring the solution at -78°C for 10 minutes, 250 mg of ammonium chloride was added and the mixture stirred for 10 minutes. The excess ammonia was removed by evaporation under a nitrogen steam. The reaction mixture was diluted with brine, extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to yield crude material 7 which was used as such in Example 7.

EXAMPLE 7

Synthesis of 7 β -Methyl-Androst-4-en-3-on-17 β -ol, t-Butyldimethylsilyl ether, (8)

To a solution of 7, from Example 6, being 432 mg in 4 ml THF was added 150 microliters DBU (1,8-diaza-bicyclo[5.4.0]undec-7-ene under nitrogen with stirring. The mixture was refluxed for 1.5 hours, then cooled, diluted with NH₄Cl solution. The solvent THF was removed under vacuum and the residue extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated under reduced pressure to yield crude material. The

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titled product 8 was purified by chromatography on silica gel using 10% EtOAc/ hexane as eluant.

EXAMPLE 8

Synthesis of 17 β -(t-butyldimethylsilyloxy)-7 β -methyl-5-oxo-A-nor-3,5-secoandrostan-3-oic acid, (9)

To a solution of 884 mg of 8 in 15 ml. t-butyl alcohol at 80°C was added 248 mg sodium carbonate in 1.5 ml water followed by a dropwise addition over 15-20 minutes of a mixture of 2.273 g sodium periodate with 16.8 mg potassium permanganate in 8 ml. water. The reaction mixture was heated at 80°C for 2 hours, cooled, filtered, the residue washed with water, and then the extract L-concentrated under vacuum. The extract was acidified with aqueous HCl, extracted with ethyl acetate and the organic layer washed with aqueous NaHSO₃, brine, dried and concentrated to yield crude 9.

The proton NMR confirmed the assigned structure.

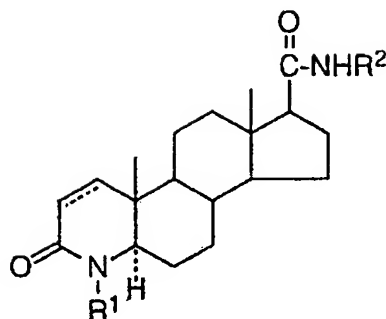
Following are descriptions and methods of synthesis of the other various 17-A radical compounds of structures IA-VIIIA, in this invention which can be used as starting materials to which the methods described herein can be applied to introduce the 16-substituent to yield the corresponding 16-substituted 17-A and 7,16-disubstituted 17-A derivatives.

EXAMPLES FOR THE CASE WHEN SUBSTITUENT "A" OF GENERAL FORMULA "I" IS AS DEFINED IN GROUP "I(A)(1)"

A preferred embodiment of the compound of general formula I is where A is structure IA (1) is represented by the general structural formula II:

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5



II

10

wherein

 R^1 is hydrogen, methyl or ethyl, and

R^2 is branched chain alkyl cycloalkyl, aralkyl of from 4-12 carbons,
phenyl, optionally substituted by methyl, chloro or fluoro,
substituted or unsubstituted 1-, 2-adamantyl, 1-, 2-
adamantylmethyl, 1-, 2- or 7-norbornanyl, 1-, 2- or 7-
norbornanymethyl.

15

Representative compounds to which the 16-substituent
may be introduced include the following:

20

17 β -(N-tert-amylcarbamoyl)-4-aza-5 α -androst-1-en-3-one,
17 β -(N-tert-hexylcarbamoyl)-4-aza-5 α -androst-1-en-3-one,
17 β -(N-tert-butylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-
3-one,

25

17 β -(N-isobutylcarbamoyl)-4-aza-5 α -androst-1-en-3-one,
17 β -(N-tert-octylcarbamoyl)-4-aza-5 α -androst-1-en-3-one,
17 β -(N-octylcarbamoyl)-4-aza-5 α -androst-1-en-3-one,
17 β -(N-t-butylcarbamoyl)-4-aza-5 α -androst-1-en-3-one,
17 β -(N-neopentylcarbamoyl)-4-aza-5 α -androst-1-en-3-one,
17 β -(N-2-adamantylcarbamoyl)-4-aza-5 α -androst-1-en-3-one,
17 β -(N-1-adamantylcarbamoyl)-4-aza-5 α -androst-1-en-3-one,
17 β -(N-2-norbornylcarbamoyl)-4-aza-5 α -androst-1-en-3-one,
17 β -(N-1-norbornylcarbamoyl)-4-aza-5 α -androst-1-en-3-one,
17 β -(N-phenylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-
one,

30

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- 17B-(N-benzylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
17B-(N-tert-amylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
5 17B-(N-tert-hexylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
17B-(N-tert-butylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
10 17B-(N-isobutylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
17B-(N-tert-octylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
17B-(N-1,1,3,3-tetramethylbutylcarbamoyl)-4-aza-5 α -androst-1-en-3-one,
15 17B-(N-octylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
17B-(N-1,1-diethylbutylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
20 17B-(N-neopentylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
17B(N-1-adamantylcarbamoyl)-4-aza-5 α -androstan-3-one;
17B(N-1-adamantylcarbamoyl)-4-methyl-4-aza-5 α -androst-1-en-3-one;
25 17B(N-1-adamantylcarbamoyl)-4-methyl-4-aza-5 α -androstan-3-one;
17B-(N-1-adamantylmethylcarbamoyl)-4-aza-5 α -androst-1-en-3-one;
17B-(N-2-adamantylcarbamoyl)-4-aza-5 α -androstan-3-one;
30 17B-(N-methyl-N-2-adamantylcarbamoyl)-4-methyl-4-aza-androstan-3-one;
17B-(N-2-adamantylcarbamoyl)-4-methyl-4-aza-5 α -androstane-3-one;
17B-(N-2-adamantylcarbamoyl)-4-methyl-4-aza-5 α -androst-1-en-3-one;

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- 17 β -(N-methyl-N-2-adamantyl)carbamoyl-4-methyl-4-aza-
androst-1-en-3-one;
17 β -(N-(3-methyl)-1-adamantyl-carbamoyl)-4-aza-4-methyl-
5 5 α -androst-an-3-one;
17 β -(N-exo-2-norbornanylcarbamoyl)-4-aza-4-methyl-5 α -
androst-1-en-3-one;
17 β -(N-exo-2-norbornanylcarbamoyl)-4-aza-5 α -androst-1-en-
3-one; 17 β -(N-2-adamantylcarbamoyl)-4-aza-5 α -
androst-en-3-one;
10 17 β -(N-methyl-N-2-adamantylcarbamoyl)-4-aza-4-methyl-
androstan-3-one;
17 β -(N-2-adamantylcarbamoyl)-4-methyl-4-aza-5 α -androstan-
3-one; and
15 17 β -(N-methyl-N-2-adamantyl)carbamoyl-4-methyl-4-aza-
androst-1-en-3-one.

The corresponding compounds of those above wherein
the 4-aza substituent is substituted in each of the above named
compounds with a hydrogen, methyl or an ethyl radical, to form a
20 different N-substituent, and wherein a double bond can be optionally
present as indicated by the dotted line in position 1.

The alkyl, cycloalkyl, aralkyl, monocyclic aryl,
1-, 2-adamantyl or 1-, 2-norbornanyl moieties can be substituted
with one or more substituents of the following: C₁-C₄
25 linear/branched alkyl, including methyl, ethyl, isopropyl, n-butyl;
nitro; oxo; C₇-C₉ aralkyl, including benzyl; (CH₂)_n COOR where n
is 0-2 and R is H or C₁-C₄ linear/branched alkyl including methyl,
ethyl; CH₂OH; OH; OR where R is C₁-C₄ linear/branched alkyl
including methyl, ethyl; halo, including fluoro, bromo, iodo; COOH;
30 COOR, where R is linear/branched C₁-C₄ alkyl; -CONH₂; CH₂NH₂;
CH₂NHCOR where R is C₁-C₄ linear/branched alkyl including
methyl, ethyl; phenyl; o, m, p-substituted phenyl including p-nitro, p-
amino and p-sulfo; or cyano. The amino group of the adamantyl or

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norbornanyl moiety can also be substituted as R^1 with methyl and ethyl, as well as hydrogen.

Also included within the scope of this invention are pharmaceutically acceptable salts or esters, where a basic or acidic group is present on the substituted alkyl, cycloalkyl, aralkyl, adamantyl or norbornanyl moiety. When an acidic substituent is present, i.e. $-COOH$, there can be formed the ammonium, sodium, potassium, calcium salt, and the like, for use as the dosage form.

Where a basic group is present, i.e. amino, acidic salts, i.e. hydrochloride, hydrobromide, acetate, pamoate, and the like, can be used as the dosage form.

Also, in the case of the $-COOH$ group being present, pharmaceutically acceptable esters can be employed, e.g. acetate, maleate, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

Representative examples include for R^2 (where AD is adamantyl):

3, 5, 7-trinitro-1-AD;
4-oxo-1-AD;
1-benzyl-1-AD; 4,4-dimethyl-1-AD; 3,7-dimethyl-5-carboxymethyl-1-AD; 3-carboxymethyl-1-AD;
3-chloro-1-AD;
1,3-dihydroxy- 6,6-dimethyl-2-AD;
3-chloro-1-AD;
4-carbethoxy-2-AD;
4-carboxy-2-AD;
3-isopropyl-1-AD;
3-n-butyl-1-AD;
3-propyl-1-AD;
3-,5-diethyl-1-AD;
3-hydroxymethyl-1-AD;
2-carboxy-1-AD;
3-methyl-1-AD;

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5-hydroxy-2-AD;
2-hydroxy-1-AD;
1-aminomethyl-1-hydroxy-2-AD;
2-oxo-1-AD;
5 2-phenyl-2-AD;
1-amino-methyl-2-AD;
1-carboxy-2-AD;
1-aminocarbonyl-2-AD;
3-hydroxy- 5,7-dimethyl-1-AD;
10 4-fluoro-1-AD;
3-fluoro-1-AD;
4-hydroxy-2-AD;
3-phenyl-1-AD;
3-(p-aminophenyl)- 1-AD;
15 3-(p-nitrophenyl)-1-AD;
3-methyl-5- hydroxymethyl-1-AD;
3,5-dimethyl-4-hydroxy-1-AD;
2-hydroxymethyl-2-AD;
3-(p-sulfophenyl)-1-AD;
20 3- methyl-5-ethyl-1-AD;
2-carboxy-2-AD;
3,5-7-trimethyl-1-AD;
4-iodo-2-AD;
4-bromo-2-AD;
25 4-chloro-2-AD;
1-acetylaminomethyl-2-AD;
1-carboxymethyl-2-AD;
1-methyl-2-AD;
1-aminocarboxylmethyl-2-AD;
30 1-aminocarboxyl-1-AD;
2-cyano-2-AD;
3,5-dimethyl- 7-ethyl-1-AD;
4-hydroxy-1-AD;
1-hydroxy-2-AD;

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5-carboxy-3-methyl-1-AD;
3,5-dimethyl-7-carboxy-1-AD;
3-carboxy-1-AD;
3-hydroxy-1-AD; and the like.

5 Representative examples include for R² as substituted
norbornanyl moieties are (where NB is norborn-anyl):

2-NB;

1,7,7-trimethyl-4-phenyl-2-NB;

3-carboxy-2-NB;

10

3-phenyl-2-carboxy-2-NB;

2-cyano-3-phenyl-2-NB;

3-hydroxy-4,7,7-trimethyl-2-NB; 6-hydroxymethyl-2-NB;

5-cyano-2-NB;

3-allyl-2-NB;

15

1-NB;

7,7-dimethyl-1-hydroxymethyl-2-NB;

3-methoxy-4,7,7-trimethyl-2-NB;

3-aminocarbonyl-2-NB;

3-ethoxycarbonyl-2-NB;

20

3,3-dimethyl-2-NB;

7-oxo-1-NB;

3-phenyl-2-NB;

1-carboxy-methyl-7,7-dimethyl-2-NB;

1-ethyl-2-NB;

25

1-methyl-2-NB;

2,2,3,3,5,5,6,6,7,7-decafluoro-1-NB;

3-hydroxy-2-NB;

3-chloro-2-NB;

3-(p-methoxyphenyl)-2-NB;

30

2,2-dimethyl-3-methylene-7-NB;

3-oxo-2-NB;

1-methoxy-2-NB;

7-NB;

3-isopropyl-2-NB;

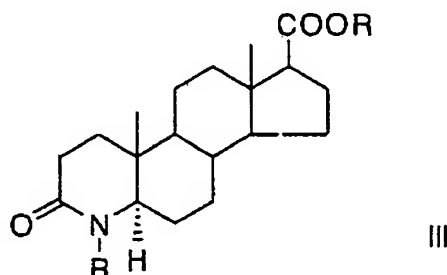
- 55 -

2-bromo-1-NB;

3-chloro-1-NB and the like.

Procedures for preparing the starting compounds of structure IA for introducing the 16-substituent including the above, are well known in the art.

The novel compounds of formula I of the present invention can be prepared by a method starting with the known steroid esters (III) of the formula:



17B-(carbomethoxy)-4-aza-5- α -androstan-3-ones which includes the stages of optionally 1) dehydrogenating said starting material to produce the corresponding compound containing a double-bond in the 1,2-position of the A-ring, 2) converting the 17-carbomethoxy substituent into an N-substituted alkyl, cycloalkyl, aralkyl, monocyclic acyl, or adamantylcarbamoyl substituent and, if desired, 3) alkylating the A-ring nitrogen to introduce a N-methyl or N-ethyl substituent into the A ring 4-position. For the dehydrogenation step, it is preferable that the 4-aza nitrogen be unsubstituted. The alternate pathways can consist of one or more discrete chemical steps and if desired can take place before step (1) or following step (1) or step (3).

In accordance with the present invention (see general flow sheet II, below at page 57), the starting materials are formed by optionally: (1) heating a 17B-alkoxycarbonyl-4-aza-5 α -androstan-3-ones, compound III, (prepared in the literature as described in the reference US Patent 4,377,584) with a dehydrogenating agent such as benzeneseleninic anhydride in a refluxing inert solvent, e.g. chlorobenzene, to form a 17B-alkoxycarbonyl-4-aza-5 α -androst-1-

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ene-3-one IV (alternately, the dichlorodicyanobenzoquinone process of Dolling, et al., JACS 1988, Vol. 110, pp. 3318-3319, can be used); (2) the formed 5 α -androst-1-en-3-one compound from Step 1 can be reacted with, e.g. sodium hydride under anhydrous conditions in a neutral solvent such as dimethylformamide; (3) contacting the resulting reaction mixture with an alkyl (methyl or ethyl) iodide to form the corresponding 17 β -alkoxy-adamantyl-carbamoyl-4-alkyl-4-aza-5 α -androst-1-en-3-one V; (4) subsequently hydrolyzing said 17 β -alkoxycarbonyl-4-alkyl-4-aza-5 α -androst-1-en-3-one with a strong base, such as aqueous methanolic potassium hydroxide at the reflux temperature, followed by acidification and isolation of the resulting steroidal acid to yield 17 β -carboxy 4-alkyl-4-aza-5 α -androst-1-en-3-one VI; (5) said steroidal acid can be then converted to its corresponding 2-pyridylthio ester by refluxing with triphenyl phosphine and 2,2'-dipyridyl disulfide in an inert solvent such as toluene and the resulting product 17 β -(2-pyridylthiocarbonyl)-4-alkyl-4-aza-5 α -androst-1-en-3-one VII can be isolated by chromatography on e.g. silica gel; and (6) said pyridylthio ester can be then reacted with 1-adamantyl-, 2-adamantylamine or norbornanyleamine in an inert solvent e.g. tetrahydro-furan, to form the desired product 17 β -N-adamantyl-carbamoyl-4-alkyl-4-aza-5 α -androst-1-en-3-one VIII which can be isolated by chromatography e.g. on silica gel. When the previous reaction is carried out in the absence of first forming the double bond at position 1, the corresponding 17 β -(N-adamantyl-carbamoyl)-4-alkyl-4-aza-5 α -androstan-3-one (or N-norbornanyl carbamoyl compound) is prepared.

In accordance with an alternate process of our invention the corresponding N-unsubstituted-17 β -(N-adamantyl-carbamoyl)-4-aza-5 α -androst-1-en-3-one XIV is readily prepared from the 17 β -(alkoxycarbonyl)-4-aza-5 α -androstone-3-one IV by repeating the above series of reaction steps but omitting the alkylation Step 2 herein above, i.e. treatment of the 4-aza-5 α -androst-1-en-3-one with

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e.g. sodium amide followed by methyl or ethyl iodide via intermediates XII and XIII.

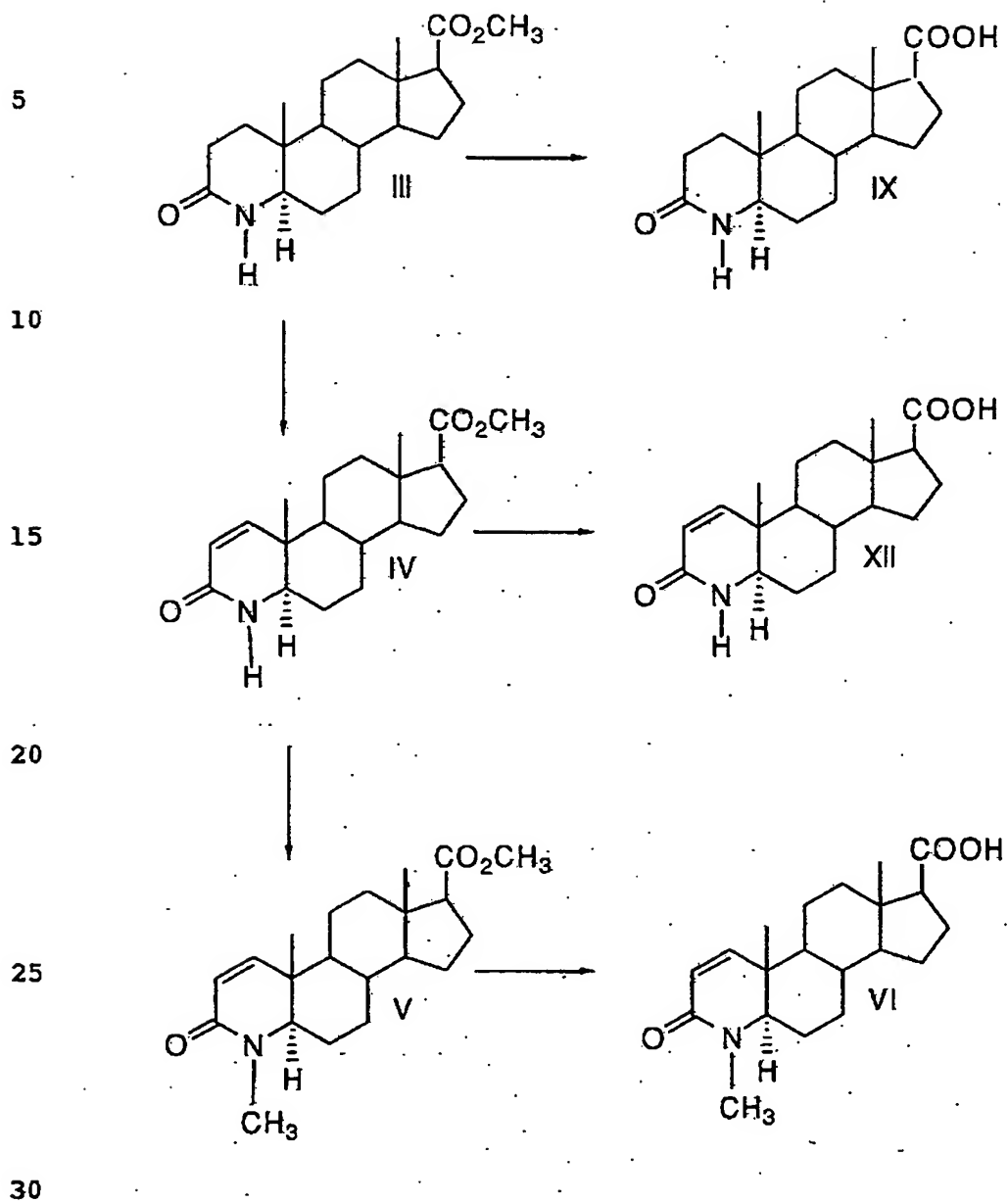
5 In accordance with a further alternate process of preparing the compounds of our invention having only hydrogen as the sole substituent on the ring A - nitrogen, the double bond in the A ring is introduced as the last step of the process. Thus, a 17 β -alkoxycarbonyl 4-aza-5 α -androstan-3-one III is hydrolyzed to the
10 corresponding steroidal acid IX 17 β -carboxy-4-aza-5 α -androstan-3-one which in turn is converted to the corresponding pyridylthio ester, 17 β (2-pyridylthiocarbonyl)-4-aza-5 α -androstan-3-one, X followed by treatment of the ester with an amine of formula R²-NH₂ wherein R² is as defined hereinabove as 1- or 2-adamantyl or 1-, 2-,
15 or 7-norbornanyl to form a 17 β (N-adamantyl-carbamoyl)-4-aza-5 α -androstone-3-one XI which is dehydrogenated as previously described to produce compound XIV, 17 β -(N-adamantyl-carbamoyl)-4-aza-androst-1-en-3-one or corresponding norbornanyl derivative.

20 In another alternate method of introducing the 17 β -(N-adamantyl-carbamoyl)substituent into a 17 β -carboxy androstane compound of formula VI, XII or IX, each is treated in a manner similar to the procedure described in Steroids, Vol. 35 #3, March 1980, p. 1-7 with dicyclohexylcarbodiimide and 1-hydroxybenzotriazole to form the 17 β -(1-benzo-triazoloxycarbonyl)-4-aza-5 α -
25 androst-1-en-3-one, VII, XIII or compound X, wherein the substituent X is benzotriazoloxo group.

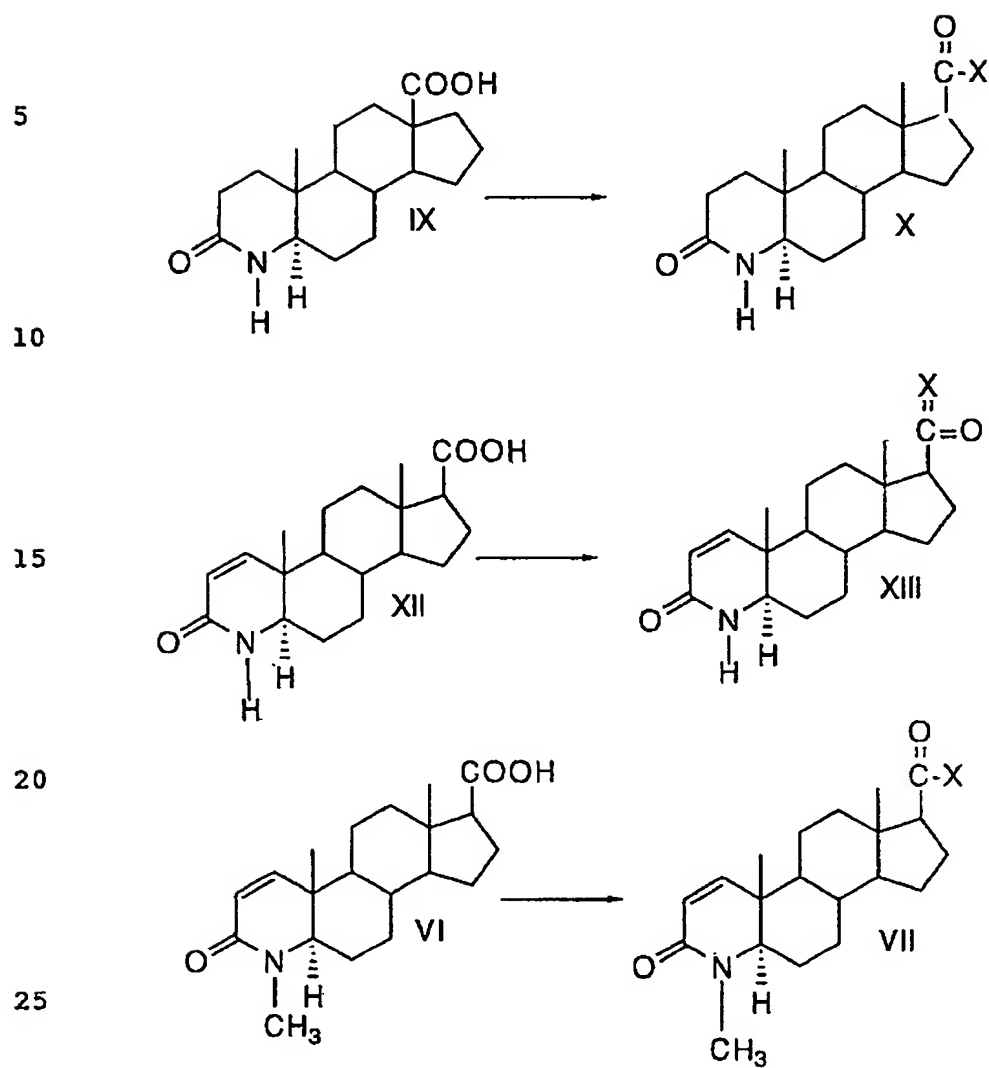
The above reactions are schematically represented in the following general flowsheet II.

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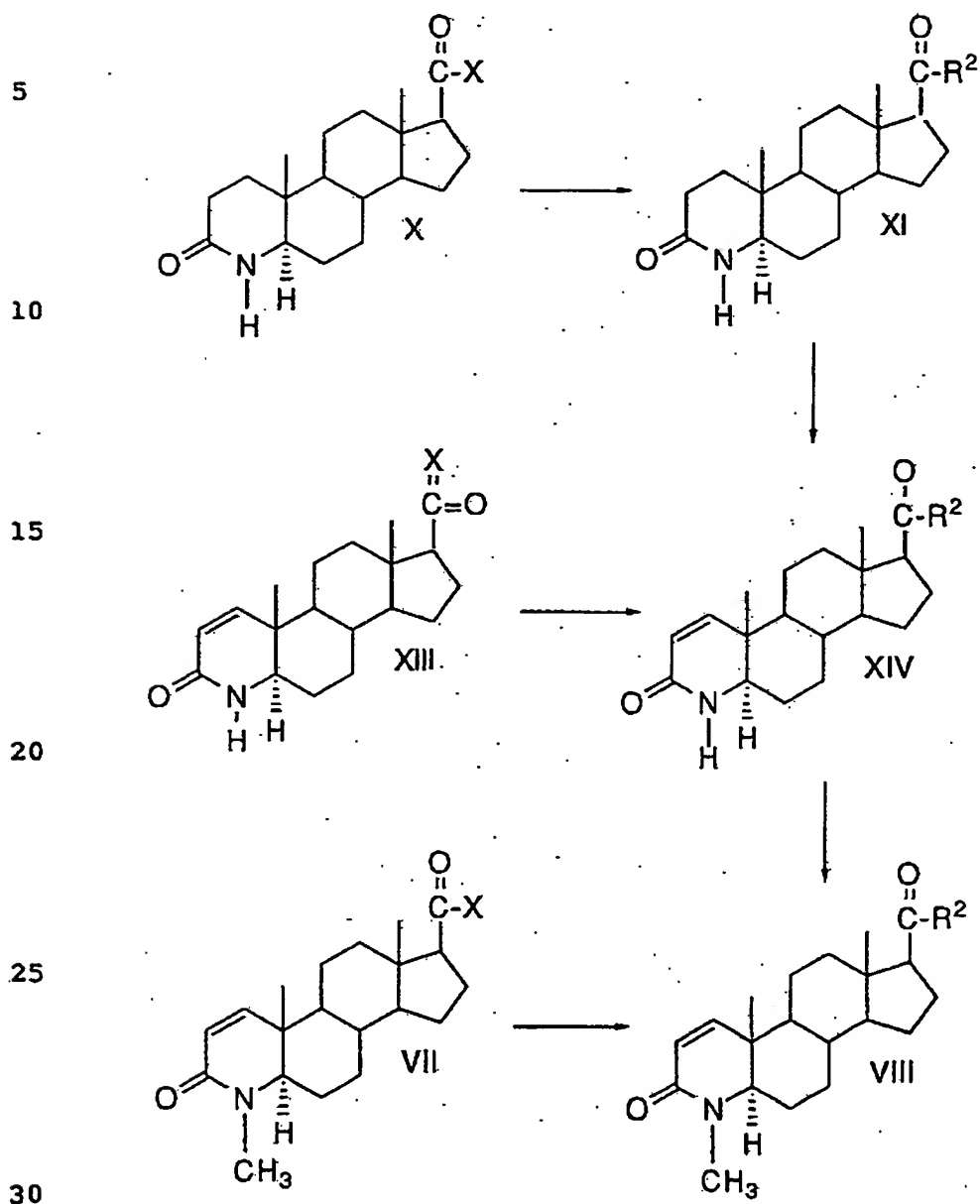
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FLWSHEET II

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GENERAL FLOWSHEET II (CONT'D)

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GENERAL FLOWSHEET II (CONTD)

X is 2-pyridylthio or 1-benzotriazoloxy.

R^2 is 1- or 2-adamantyl or norbornanyl.

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EXAMPLES FOR THE CASE WHEN SUBSTITUENT "A" OF
GENERAL FORMULA "I" IS AS DEFINED IN GROUP "I(A)(2)"

5 Another preferred embodiment of the compounds
of our invention is the compound of above general structure I,
wherein the dotted line between the A ring positions 1 and 2 is a
double bond,

R is hydrogen or methyl, and

10 "A" is COQ where "Q" is branched chain alkyl, or cycloalkyl
of from 4-10 carbons.

Another embodiment of the invention is the compounds of above
Structure I where "Q" is phenyl, or phenyl substituted by substituents
described above, including where

15 Q is phenyl, 2-, 3-, or 4-tolyl, xylyl, 2-bromophenyl, 2-
chlorophenyl, 2,6-dichlorophenyl, 2,6-dibromophenyl,
aminophenyl, N-alkylaminophenyl, N-N-dialkyl-
aminophenyl, 4-biphenyl, 3-biphenyl, naphthyl,
anthracyl, phenanthryl, thiophenyl, methylthiophenyl,
20 methylsulfinyl, phenyl, methylsulfofenyl,
aminosulfofenyl, thioethylphenyl,
acetoxymethylthiophenyl, 17 β -(4-hydroxyphenyl), 17 β -
(3-hydroxyphenyl), 17 β -(3,4-dihydroxyphenyl), or 17 β -
(3,5-dimethyl-4-hydroxyphenyl).

25 Representative compounds of the invention are:

17 β -(phenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-ene-3-one;
17 β -(2-tolylcarbonyl)-4-aza-4-methyl-5 α -androst-1-ene-3-one;
17 β -(3-tolylcarbonyl)-4-aza-4-methyl-5 α -androst-1-ene-3-one;
17 β -(4-tolylcarbonyl)-4-aza-4-methyl-5 α -androst-1-ene-3-one;
30 17 β -(2-bromophenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-ene-
3-one;
17 β -(2-chlorophenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-ene-
3-one;
17 β -(2,6-dichlorophenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-
ene-3-one;

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- 17 β -(2,6-dibromophenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-ene-3-one;
- 17 β -(xylylcarbonyl)-4-aza-4-methyl-5 α -androst-1-ene-3-one;
- 17 β -(t-butylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 5 17 β -(isobutylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(isooctylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(n-octylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(1,1-diethylbutylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(neopentylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 10 17 β -(tert-amylcarbonyl)-4-aza-4-5 α -androst-1-ene-3-one;
- 17 β -(tert-hexylcarbonyl)-4-aza-4-5 α -androst-1-ene-3-one;
- 17 β -(cyclohexylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(cyclopentylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(benzylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 15 17 β -(2-pyridylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(4-pyridylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(2-pyrrolylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(2-furylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 20 17 β -(2-thiophenylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(2-adamantylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(phenylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(2-tolylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(3-tolylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 25 17 β -(4-tolylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(2-bromophenylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(2-chlorophenylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(2,6-dichlorophenylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(2,6-dibromophenylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 30 17 β -(xylylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(phenylethyl)carbonyl-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(4-dimethylaminophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
- 17 β -(3-dimethylaminophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one.

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- 17 β -(3,4-diethylaminophenylcarbonyl)-4-aza-androst-1-en-3-one.
17 β -(3,5-dimethyl-4-diethylaminophenylcarbonyl)-4-aza-5 α -
androst-1-en-3-one;
5 17 β -(4-N-methylaminomethylphenylcarbonyl)-4-aza-5 α -androst-
1-en-3-one; or
17 β -(2-N-ethylamino-4-ethylphenylcarbonyl)-4-aza-5 α -androst-
1-en-3-one;
17 β -(4-phenylbenzoyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(3-phenylbenzoyl)-4-aza-5 α -androst-1-en-3-one;
10 17 β -(4-biphenyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(3-biphenyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(1-naphthyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(2-naphthyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(1-phenanthryl)-4-aza-5 α -androst-1-en-3-one;
15 17 β -(2-phenanthryl)-4-aza-5 α -androst-1-en-3-one;
17 β -(1-biphenyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(9-anthracyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(4-thiophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(3-thiophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
20 17 β -(4-methylthiophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(4-methylsulfinylphenylcarbonyl)-4-aza-5 α -androst-1-en-3-
one;
17 β -(4-methylsulfophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(3-methylsulfinylphenylcarbonyl)-4-aza-5 α -androst-1-en-3-
25 one;
17 β -(4-N,N-dimethylaminosulfophenylcarbonyl)-4-aza-5 α -
androst-1-en-3-one;
17 β -(2-ethyl-4-methylthiophenylcarbonyl)-4-aza-5 α -androst-1-
en-3-one;
30 17 β -(4-thioethylphenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-
en-3-one;
17 β -(4-acetoxymethylthiophenylcarbonyl)-4-aza-4-methyl-5 α -
androst-1-en-3-one;

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- 17B-(2-methyl-4-methylthiophenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 17B-(2-methyl-4-methylsulfinylphenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 5 17B-(2-isopropyl-4-methylsulfofphenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 17B-(4-methylthiophenylcarbonyl)-4-aza-4-methyl-5 α -androstan-3-one;
- 10 17B-(4-methylsulfinylphenylcarbonyl)-4-aza-4-methyl-5 α -androstan-3-one;
- 17B-(4-methylsulfofphenylcarbonyl)-4-aza-4-methyl-5 α -androstan-3-one;
- 17B-(4-hydroxyphenyl)-4-aza-5 α -androst-1-en-3-one;
- 15 17B-(3-hydroxyphenyl)-4-aza-5 α -androst-1-en-3-one;
- 17B-(3,4-dihydroxyphenyl)-4-aza-5 α -androst-1-en-3-one;
- 17B-(3,5-dimethyl-4-hydroxyphenyl)-4-aza-5 α -androst-1-en-3-one;
- 17B-(4-hydroxymethylphenyl)-4-aza-5 α -androst-1-en-3-one;
- 20 17B-(2-hydroxyethylphenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
- 17B-(4-methoxyphenyl)-4-aza-5 α -androst-1-en-3-one;
- 17B-(4-carboxymethylphenyl)-4-aza-5 α -androst-1-en-3-one;
- 17B-(4-hydroxyphenyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 25 17B-(3-hydroxyphenyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 17B-(3,4-dihydroxyphenyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 17B-(3,5-dimethyl-4-hydroxyphenyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 30 17B-(4-hydroxymethylphenyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 17B-(2-hydroxyethylphenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 17B-(4-methoxyphenyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;

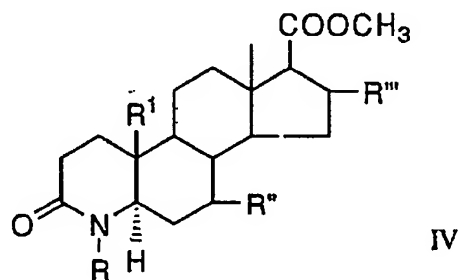
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17 β -(4-carboxymethylphenyl)-4-aza-4-methyl-5 α -androst-1-en-3-one; and

17 β -(4-carboxyphenyl)-4-aza-5 α -androst-1-en-3-one;

and the corresponding compounds wherein the 4-hydrogen substituent is replaced in each of the above named compounds by a methyl or an ethyl radical.

The compounds of formula I of the present invention can be prepared by a method starting with the known steroid ester of the formula:



named 17 β -(carbomethoxy)-4-aza-5 α -androstan-3-one, which includes the stages of (1) dehydrogenating said starting material to produce the corresponding compound containing a double bond in the 1,2-position of the A-ring, (2) converting the 17-carbomethoxy substituent into a 17 β -acyl substituent and, if desired (3) alkylating the A-ring nitrogen to introduce 4-methyl or 4-ethyl substituents into the A-ring. For the dehydrogenation step, it is preferable that the 4-aza nitrogen be unsubstituted. The dehydrogenation step can be carried out, e.g. according to the procedure of Dolling, et al. involving dichlorodicyanobenzo-quinone, JACS (1988) Vol. 110, pp. 3318-3319. Stage (2) may consist of one or more chemical steps and if desired may take place before stage (1) or following stage (1) or stage (3).

In accordance with a further alternate process of preparing the compounds of our invention, having only hydrogen as the sole substituent on the ring A-nitrogen, the 1,2-double bond in the A-ring is introduced as the last step of the process. Thus, with reference to the flow sheet below on page 66, a 17 β -

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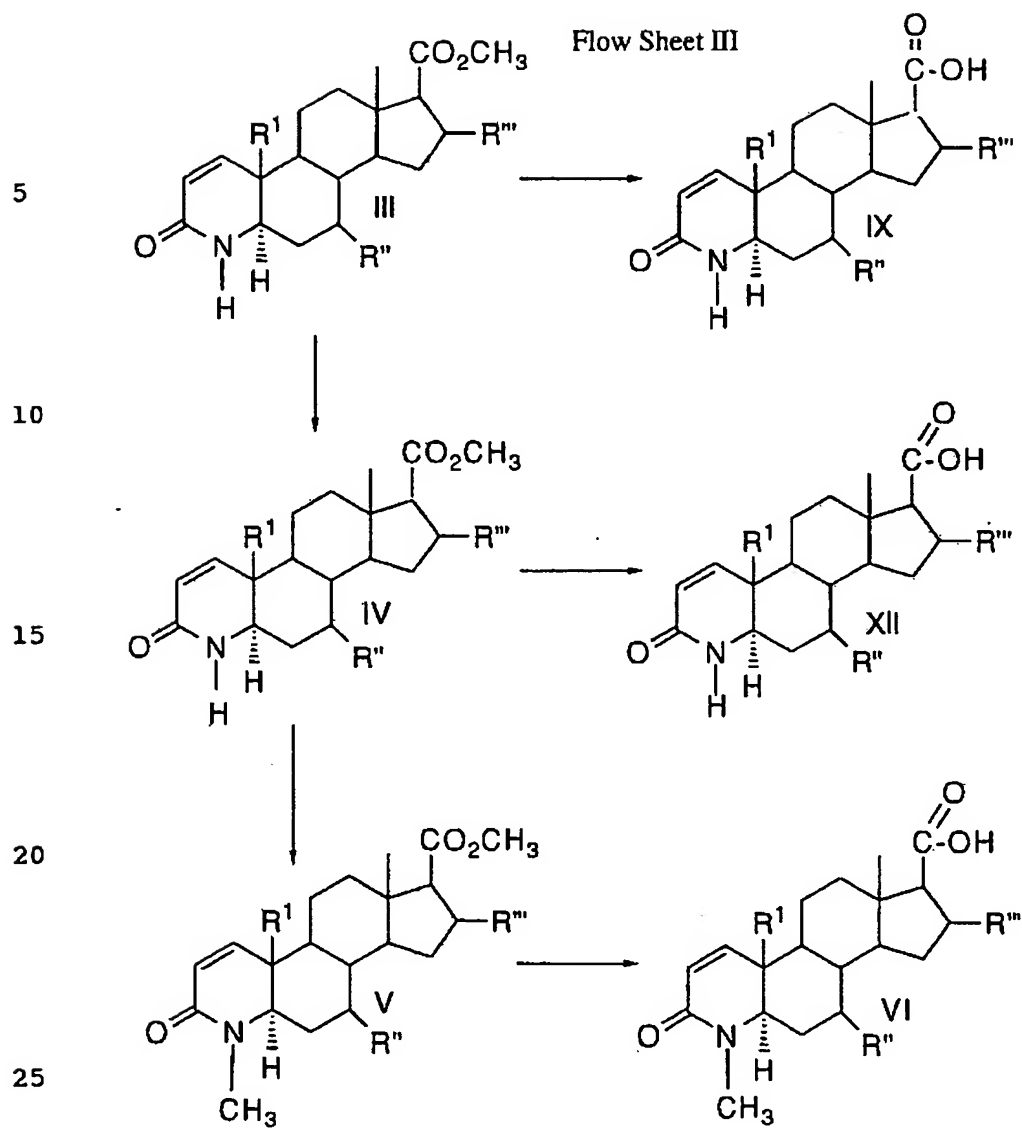
alkoxycarbonyl-4-aza-5 α -androstan-3-one (III) is hydrolyzed to the corresponding steroidal acid, 17 β -carboxy-4-aza-5 α -androstan-3-one, (IX) which, in turn, is converted to the corresponding thiopyridyl ester, 17 β -(2-pyridylthiocarbonyl)-4-aza-5 α -androstan-1-one (X) followed by treatment of the ester with an R²MgX or R²Li compound wherein R² is as defined hereinabove to form a 17 β -(acyl)-4-aza-5 α -androstan-3-one (XI) which is dehydrogenated as previously described to produce compound XIV, 17 β -(acyl)-4-aza-5 α -androst-1-en-3-one.

In an additional alternative process for making the compounds of formula I when the starting material is an ester, particularly methyl ester as shown in formula III-V in the schematic, reaction with a Grignard reagent R²MgX, gives the ketone, 17 β -R²CO-, corresponding to the R² moiety associated with the Grignard reagent.

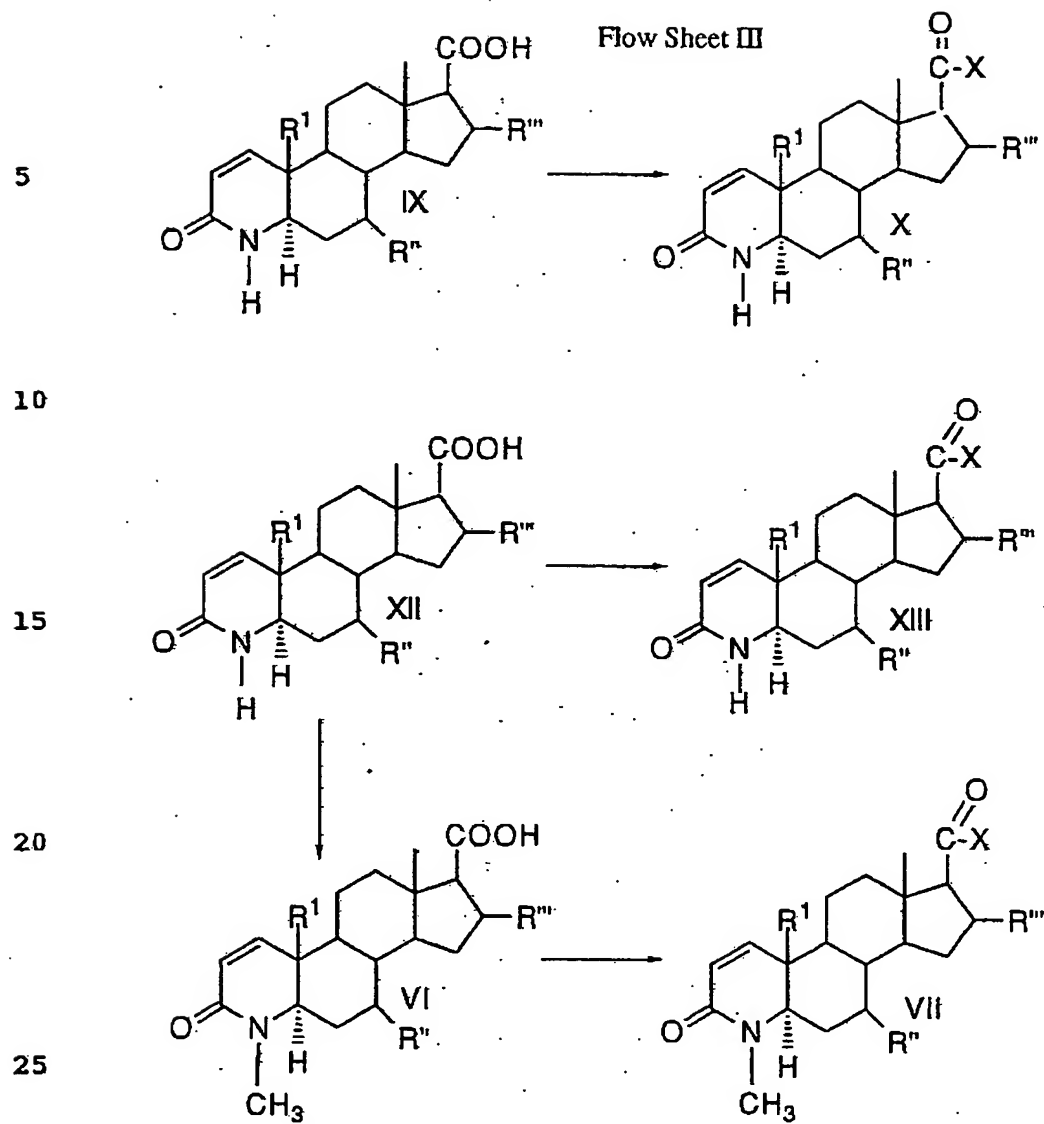
The above reactions are schematically represented in the following general flowsheet III:

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Flow Sheet III

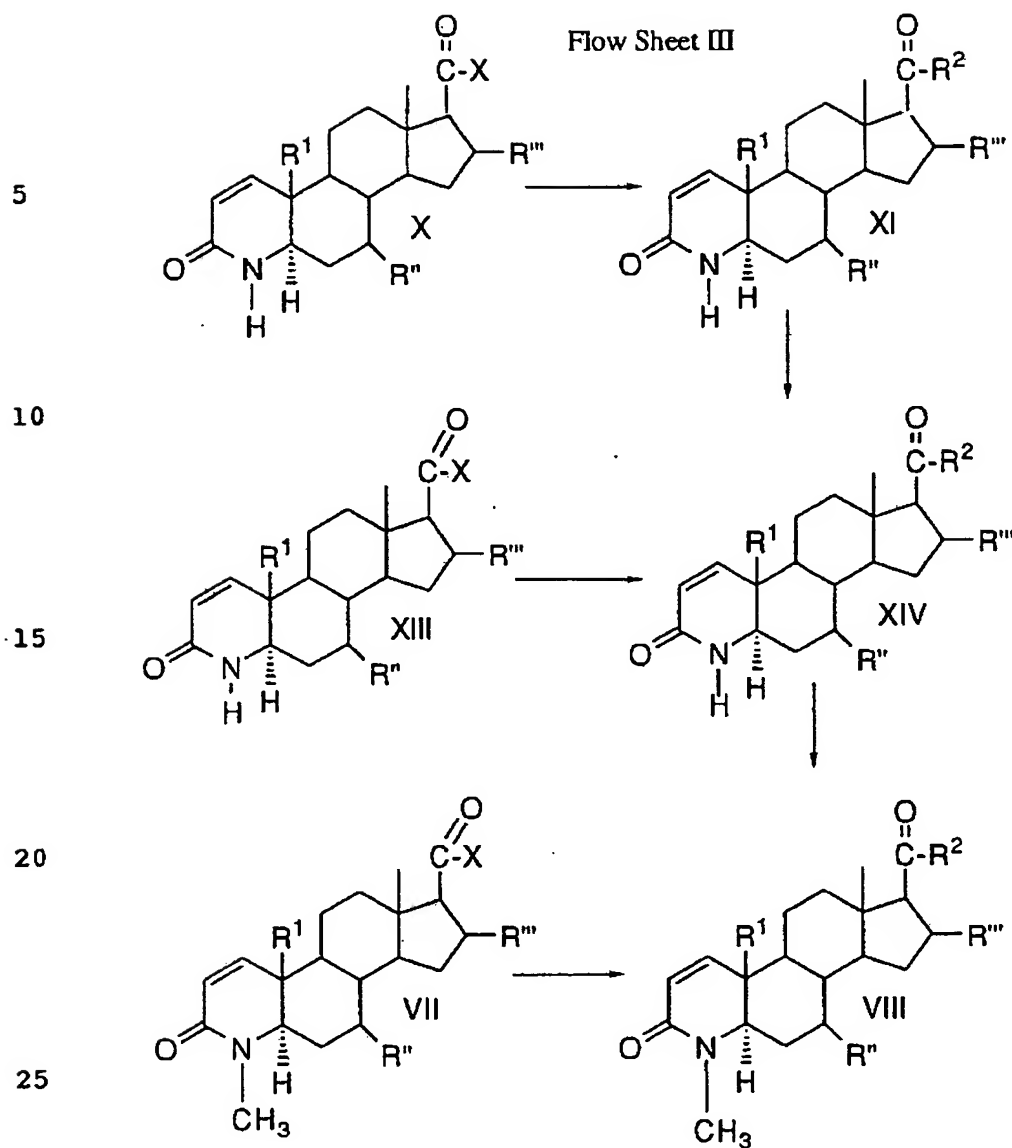


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Flow Sheet III



X is 2-pyridylthio

30

wherein X is a 2-pyridylthio substituent and R² is defined as hereinabove.

In the above described flowsheet, where R² is p-hydroxybiphenyl, this can be derived by starting with an appropriate bromobiphenylphenol, e.g. p-bromobiphenylphenol, protecting the

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phenolic -OH with a conventional blocking group, e.g. triorganosilyl, i.e. t-butyldimethylsilyl, carrying out the Grignard reaction and then deblocking the silyl group by the use of, e.g. refluxing aqueous tetrabutylammonium fluoride.

5 Other halo substituted benzenes to form the appropriate Grignard reagent useful in the instant invention will be obvious to one skilled in the art from this disclosure.

By the term "protected hydroxy" as used herein, is meant the alcoholic or carboxylic -OH groups which can be protected by conventional blocking groups in the art as described in "Protective Groups In Organic Synthesis" by Theodora W. Greene, Wiley-Interscience, 1981, New York. Preferred are the triorganosilyl groups, e.g. t-butyldimethylsilyl, phenyldimethylsilyl, diphenylmethylsilyl, and the like.

15 By the term " C_1 - C_4 alkyl" is used herein, is meant linear or branched alkyl, including methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl and t-butyl.

When this reaction scheme is carried out using an R^2MgX or R^2Li compound containing an thiophenyl substituted R^2 , e.g. p-methylthiophenyl magnesium chloride, the corresponding 17 β -(substituted thio-benzoyl)-4-alkyl-4-aza-5 α -androst-1-en-3-one is prepared wherein phenyl is R^2 .

20 The Grignard reagent, R^2MgX , for all the species included within the scope of this invention, are available or can readily be made by one skilled in the art. For example, where R^2 is C_1 - C_4 alkyl thiophenyl, can be formed from the appropriate C_1 - C_4 alkyl thiobromobenzene, e.g. p-methylthiobromobenzene.

The formed C_1 - C_4 alkyl thiobenzene can be used to further prepare C_1 - C_4 alkyl sulfoxides by oxidation with e.g. m-chloroperbenzoic acid. The resulting sulfoxide can be further oxidized by the use of the m-chloroperbenzoic acid reaction to proceed for a longer period of time to form the C_1 - C_4 alkyl sulfone.

30 Further, the sulfoxide can be used in the Pummerer rearrangement to form the corresponding thiol.

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The $-\text{SO}_2\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})_2$ substituted phenyl (R^2) is formed from the appropriate bromobenzene, e.g. p-N,N-dimethylaminosulfobromobenzene which is used directly in the Grignard reaction to form the final product.

5 The thioalkyl groups on the phenyl ring, i.e. $-(\text{CH}_2)_m\text{SH}$, where m is 1-4, are readily formed via a four step procedure from an alkoxy alkyl phenyl bromide, $\text{Br-C}_6\text{H}_4-(\text{CH}_2)_m\text{OCH}_3$. Direct addition of the Grignard reagent prepared from above-bromoalkyl phenyl derivative to the thiopyridyl ester results in the keto derivative, i.e. 17 β -(4-methoxyalkyl-benzoyl)-4-aza-5 α -androst-1-ene-3-one. This can be readily converted into thio analogue via BBr_3 at -70°C to form the hydroxyalkyl derivative, followed by displacement by halogen, e.g. bromo and then
15 converting the halogenated compound through NaSH displacement to give the final mercapto compound. Where in the Reaction Scheme said pyridylthio ester is reacted with an aminophenyl containing R^2 -Li or an R^2MgX ($\text{X}=\text{Cl}, \text{Br}$) compound, such as p-dimethylaminophenyl magnesium chloride, this is carried out in
20 tetrahydrofuran to form the desired product 17 β -(p-dimethylaminophenyl-carbonyl)-4-alkyl-4-aza-5 α -androst-1-en-3-one (VIII) which is isolated by chromatography on silica gel.

The Grignard reagent, R^2MgX , for all of the aminophenyl species included within the scope of this invention, are
25 available and can be made readily by one skilled in the art.

Where in the process said Grignard reagent contains a phenolic type R^2 moiety, then said pyridylthio ester is then reacted with an R^2 -Li or an R^2MgX ($\text{X}=\text{Cl}, \text{Br}$) Grignard reagent, such as p-methoxyphenyl-magnesium chloride in tetrahydrofuran to form
30 the desired product, e.g. 17 β -(p-methoxy-phenylcarbonyl)-4-alkyl-4-aza-5 α -androst-1-en-3-one (VIII) which is isolated by chromatography on silica gel. When this reaction is carried out using another R^2MgX or, an R^2 -Li compound in place of p-methoxyphenylmagnesium chloride, the corresponding 17 β -

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(substituted benzoyl)-4-alkyl-4-aza-5 α -androst-1-en-3-one is prepared wherein phenyl is R².

5 The Grignard reagent, R²MgX, for all of the species included within the scope of this invention, are available and can be made readily by one skilled in the art.

For example, where R² is hydroxyphenyl, this can be derived by starting with an appropriate bromophenol, e.g. p-bromophenol, protecting the phenolic -OH with a conventional blocking group, e.g. triorganosilyl, i.e. t-butyldimethylsilyl, carrying
10 out the Grignard reaction and then deblocking the silyl group by the use of, e.g. refluxing aqueous tetrabutylammonium fluoride.

For R² being hydroxyethylphenyl, the same blocking procedure can be analogously conducted starting with the appropriate hydroxyalkyl bromophenol, e.g. p-hydroxymethyl-
15 bromobenzene, or p-hydroxyethylbromobenzene.

Where R² is carboxyphenyl, this can be obtained by the chromic acid oxidation of the appropriate hydroxymethylbenzene, e.g. p-bromo-hydroxymethylbenzene, formed as described above.

Where R² is -O-C₁-C₄ alkyl, the appropriate bromo-O-
20 C₁-C₄ alkyl benzene, e.g. p-methoxybromobenzene, is utilized for the Grignard reaction.

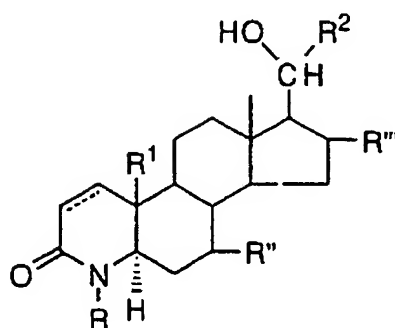
Other halo substituted benzenes to form the appropriate Grignard reagent useful in the instant invention will be obvious to
25 one skilled in the art from this disclosure.

By the term "protected hydroxy" as used herein, is meant the alcoholic or carboxylic -OH groups which can be protected by conventional blocking groups in the art as described in "Protective Groups In Organic Synthesis" by Theodora W. Greene,
30 Wiley-Interscience, 1981, New York. Preferred are the triorganosilyl groups, e.g. t-butyl-dimethylsilyl, phenyldimethylsilyl, diphenylmethylsilyl, and the like.

Also within the scope of the present invention is the use of ketone reduction products of I, in combination with minoxidil for

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treatment of patterned alopecia, being secondary alcohols of the formula:



General Structural Formula V

wherein R is selected from hydrogen, methyl and ethyl;

R^2 is (a) a monovalent radical selected from straight or branched chain alkyl, or cycloalkyl, of from 1-12 carbons, which can be substituted by one or more of C_1 - C_2 alkyl or halo;

(b) an aralkyl radical selected from benzyl or phenethyl;

(c) a polycyclic aromatic radical which can be substituted with one or more of: -OH, protected -OH, - OC_1 - C_4 alkyl, C_1 - C_4 alkyl, halo or nitro;

(d) a monocyclic aromatic radical which can be substituted with one or more of:

(1) -OH, - OC_1 - C_4 alkyl, C_1 - C_4 alkyl, $-(CH_2)_mOH$, $-(CH_2)_nCOOH$, including protecting hydroxy, where m is 1-4, n is 1-3, providing C_1 - C_4 alkyl is only present when one of the above oxygen-containing radicals is present;

(2) -SH, - SC_1 - C_4 alkyl, - SOC_1 - C_4 alkyl, - SO_2C_1 - C_4 alkyl, - $SO_2N(C_1$ - C_4 -alkyl) $_2$, C_1 - C_4 alkyl $-(CH_2)_mSH$, -S- $(CH_2)_n$ -O-COCH $_3$, where m is 1-4 n is 1-3, providing C_1 - C_4 alkyl is only present when one of the above sulfur containing radicals is present;

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(3) $N(R^3)_2$, which can be protected, where R^3 is independently H or C_1-C_4 alkyl, where the monoaryl ring can also be further substituted with C_1-C_4 alkyl; and

(4) heterocyclic radical selected from 2- or 4-pyridyl, 2-pyrrolyl, 2-furyl or thiophenyl;

R' , R'' and R''' are hydrogen or methyl, wherein the dotted line represents a double bond which can be present, and pharmaceutically acceptable salts and esters thereof.

These compounds can be made by conventional sodium borohydride reduction of the carbonyl attached to R^2 without reducing the amide carbonyl in Ring A or the 1,2-double bond, if present. If the R^2 phenyl contains a carbonyl function, it can be selectively blocked and then regenerated after the borohydride reduction by conventional methods.

The borohydride reduction can be carried out in, e.g. water or aqueous methanol, at a temperature of room temperature to 50°C and the product then isolated and purified by conventional means. The compounds are also active as 5- α reductase inhibitors in the treatment of patterned alopecia.

EXAMPLES FOR THE CASE WHEN SUBSTITUENT "A" OF GENERAL FORMULA "I" IS AS DEFINED IN GROUP "II(A)"

DESCRIPTION WHERE A IS IIA

Another preferred embodiment of the invention is

where;

Z is $-XR^4$, or $-(CHR^1)_n-XR^4$;

n is 1-10;

X is $-O-$ or $-S(O)_p-$,

wherein p is zero, 1 or 2; and

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R^1 can be the same or different when n is greater than 1 and is -H, aryl, or $-C_{1-3}$ alkyl unsubstituted or substituted with aryl;

R is -H, methyl or ethyl;

5 R^4 is 1) $-C_{1-20}$ alkyl, unsubstituted or substituted with one or more of:

- a) -OH,
- b) halo,
- 10 c) $-C_{1-8}$ alkoxy,
- d) $-C_{1-6}$ alkenyl,
- e) $-\text{CONR}^5\text{R}^5$, wherein R^5 is independently
 - i) -H,
 - 15 ii) $-C_{1-8}$ alkyl unsubstituted or substituted with one or more of R^7 , aryl or heterocycle, the aryl being unsubstituted or substituted with one or more of R^7 or R^9 ,
 - iii) aryl unsubstituted or substituted with one or more of R^7 or R^9 , or
 - 20 iv) heterocycle, unsubstituted or substituted with one or more of R^7 or R^9 ,
- f) $-\text{COOR}^6$, wherein R^6 is
 - i) -H,
 - 25 ii) $-C_{1-8}$ alkyl unsubstituted or substituted with one or more of R^7 or aryl, the aryl being unsubstituted or substituted with one or more of R^7 or R^9 , or
 - iii) aryl, unsubstituted or substituted with one or more of R^7 or R^9 ,
- g) $-\text{S}(\text{O})_p-\text{R}^5$, wherein p is defined above,
- 30 h) $-\text{N}(\text{R}^5)_2$,
 - i) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9 ,
 - j) heterocycle, unsubstituted or substituted with one or more of R^7 or R^9 ,

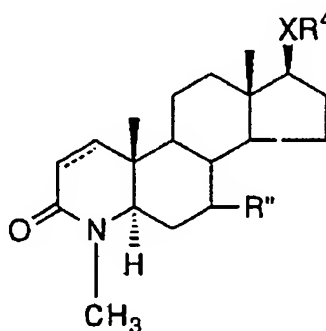
- 76 -

- k) $-C_{3-10}$ cycloalkyl, such as cyclohexyl, norbornyl, or adamantyl, unsubstituted or substituted with one or more of R^7 or R^9 , or
- 5 l) $-\text{CONR}^8-\text{CO}-\text{NHR}^8$, wherein R^8 is $-\text{H}$, $-C_{1-8}$ alkyl, benzyl or cyclohexyl; or
- 2) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9 , or
- 3) heterocycle or $-C_{3-10}$ cycloalkyl, either of which is
- 10 unsubstituted or substituted with one or more of R^7 or R^9 ;
- R^7 is 1) $-\text{OH}$,
2) $-C_{1-3}$ alkoxy,
3) $-\text{CN}$,
15 4) $-\text{COOR}^6$
5) $-C_{1-8}$ alkyl- COOR^6
6) $-\text{NO}_2$, or
7) $-\text{halo}$; and
8) amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino;
- 20 R^9 is 1) $-C_{1-8}$ alkyl, unsubstituted or substituted with one or more of aryl or R^7 ,
2) $-\text{CO}-\text{A}$, $-C_{1-8}$ alkyl- $\text{CO}-\text{A}$, $-\text{NHCO}-\text{A}$, or $-\text{S}(\text{O})_p-\text{A}$, wherein p is defined above and A is
- 25 a) $-\text{H}$,
b) $-C_{1-8}$ alkyl, unsubstituted or substituted with one or more of
- i) $-R^7$, or
ii) aryl, unsubstituted or substituted with one or more of R^7 , or
- 30 c) aryl, unsubstituted or substituted with one or more of R^7 ,
3) $-\text{NHCO}$ -heterocycle,
4) $-\text{N}(\text{R}^{10})_2$ or $-\text{CON}(\text{R}^{10})_2$ wherein R^{10} is independently $-\text{H}$, heterocycle, or $-\text{A}$,

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5) $\text{-NHCO-(CH}_2\text{)}_q\text{-CO-Q}$, wherein q is 1-4, and Q is $\text{-N(R}^{10}\text{)}_2$ or -OR^{10} .

Another preferred embodiment of this invention is represented by compounds of general structural formula VI:



VI

wherein R^4 is -C_{1-20} alkyl, unsubstituted or substituted with one or more of

-OH , halo, -C_{1-8} alkoxy, -C_{1-6} alkenyl, $\text{-S(O)}_p\text{-R}^5$, $\text{-N(R}^5\text{)}_2$, aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9 , heterocycle unsubstituted or substituted with one or more of R^7 or R^9 , or -C_{3-10} cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9

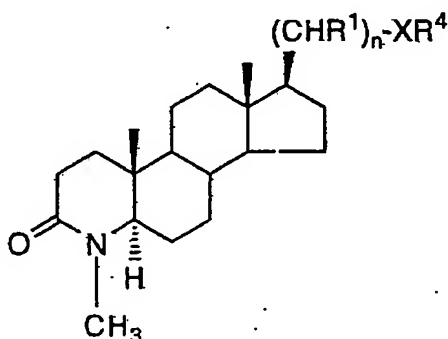
and X , p , R^5 , R^7 and R^9 are all defined as in general structural formula I.

Another preferred embodiment of this invention is represented by compounds of general structural formula VI wherein R^4 is -C_{1-20} alkyl substituted with $\text{-CONR}^5\text{R}^5$, -COOR^6 or $\text{-CONR}^8\text{CONHR}^8$, and X , R^5 , R^6 and R^8 are defined as in general structural formula I.

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Another preferred embodiment of this invention is represented by compounds of general structural formula VI wherein R^4 is aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9 ; heterocycle unsubstituted or substituted with one or more of R^7 or R^9 ; or $-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9 ; and X, R^7 and R^9 are defined as in general structural formula I.

Another preferred embodiment of this invention is represented by compounds of general structural formula VII:



VII

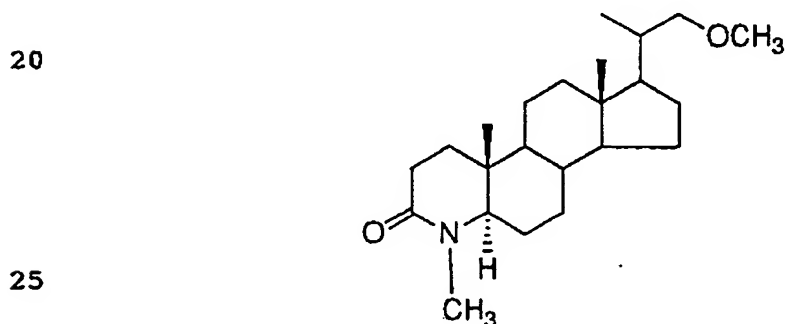
wherein R^4 is $-C_{1-20}$ alkyl, unsubstituted or substituted with one or more of $-OH$, halo, $-C_{1-8}$ alkoxy, $-C_{1-6}$ alkenyl, $-S(O)_p-R^5$, $-N(R^5)_2$, aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9 , heterocycle unsubstituted or substituted with one or more of R^7 or R^9 , or $-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9 , and X, R^1 , n, p, R^5 , R^7 and R^9 are defined as in general structural formula I.

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Another preferred embodiment of this invention is represented by compounds of general structural formula VII wherein R^4 is $-C_{1-20}$ alkyl substituted with $-\text{CONR}^5R^5$, $-\text{COOR}^6$ or $-\text{CONR}^8\text{CONHR}^8$,
5 and X, R^1 , n, R^5 , R^6 and R^8 are defined as in general structural formula I.

Another preferred embodiment of this invention is represented by compounds of formula VII wherein R^4 is aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9 ; heterocycle unsubstituted or substituted with one or more of R^7 or R^9 ; or $-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9 ; and X, R^1 , n, R^7 and R^9 are defined as in general
15 structural formula I.

Novel compounds of the present invention include but are not limited to the following compounds:

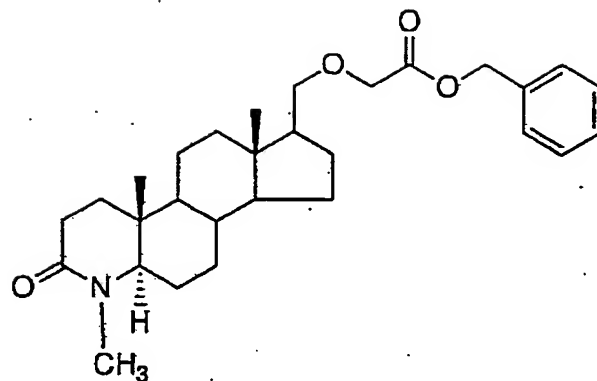


20-(methoxymethyl)-4-methyl-5 α -4-azapregnan-3-one,

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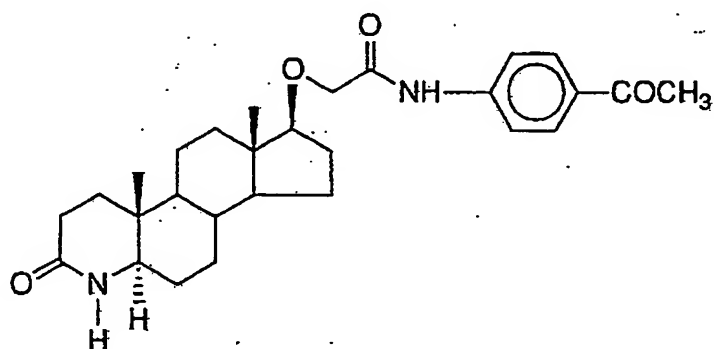
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17-(carbobenzyloxymethoxymethyl)-4-methyl-5 α -4-azaandrostan-3-one,

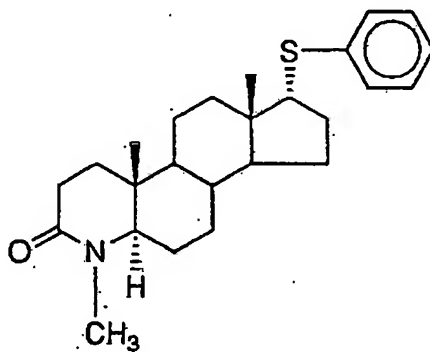
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5 α -4-azaandrostan-3-on-17 β -yloxy-N-(4-acetylphenyl)acetamide,

25



30

17 α -thiophenoxy-4-methyl-5 α -4-azaandrostan-3-one,
17-(methoxymethyl)-4-methyl-5 α -4-azaandrostan-3-one,

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- 17-(ethylthiomethyl)-4-methyl-5 α -4-azaandrostan-3-one,
17-(carboxymethoxymethyl)-4-methyl-5 α -4-azaandrostan-3-one,
17-(carboethoxymethoxymethyl)-4-methyl-5 α -4-azaandrostan-3-
one,
5 17-(carbobenzyloxymethoxymethyl)-4-methyl-5 α -4-
azaandrostan-3-one,
17-(diphenylmethoxymethyl)-4-methyl-5 α -4-azaandrostan-3-one,
20-(diphenylmethoxy)-4-methyl-5 α -4-azapregnan-3-one,
20-(methoxy)-4-methyl-5 α -4-azapregnan-3-one,
10 20-(methoxymethyl)-4-methyl-5 α -4-azapregnan-3-one,
20-(diphenylmethoxymethyl)-4-methyl-5 α -4-azapregnan-3-one,
20-(ethylthiomethyl)-4-methyl-5 α -4-azapregnan-3-one,
20-(isopropylthiomethyl)-4-methyl-5 α -4-azapregnan-3-one,
15 ethyl 4-methyl-5 α -4-azaandrostan-3-on-17 β -yloxyacetate,
diphenylmethyl 4-methyl-5 α -4-azaandrostan-3-on-17 β -
yloxyacetate,
4-methyl-5 α -4-azaandrostan-3-on-17 β -yloxy-N-(3,4-
dihlorobenzyl)acetamide,
20 4-methyl-5 α -4-azaandrostan-3-on-17 β -yloxy-N-phenylacetamide,
4-methyl-5 α -4-azaandrostan-3-on-17 β yloxyacetic acid,
4-methyl-5 α -4-azaandrostan-3-on-17 β -yloxy-N-(4-
acetylphenyl)acetamide,
25 4-methyl-5 α -4-azaandrostan-3-on-17 β -yloxyacetamide,
17 β -(4-biphenyloxy)-4-methyl-5 α -4-azaandrostan-3-one,
17 β -(2,4-dinitrophenoxy)-4-methyl-5 α -4-azaandrostan-3-one,
4-methyl-17 α -phenoxy-5 α -4-azaandrostan-3-one,
17 α -(4-biphenyloxy)-4-methyl-5 α -4-azaandrostan-3-one,
30 17 β -diphenylmethoxy-4-methyl-5 α -4-azaandrostan-3-one,
4-methyl-17 α -thiophenoxy-5 α -4-azaandrostan-3-one,
4-methyl-17 α -phenylsulfonyl-5 α -4-azaandrostan-3-one,
4-methyl-17 α -phenylsulfinyl-5 α -4-azaandrostan-3-one (isomer
a),

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- 4-methyl-17 α -phenylsulfinyl-5 α -4-azaandrostan-3-one (isomer b),
4-methyl-17 β -(4-nitrophenoxy)-5 α -4-azaandrostan-3-one,
17 β -(4-aminophenoxy)-4-methyl-5 α -4-azaandrostan-3-one
5 hydrochloride,
17 β -(4-acetamidophenoxy)-4-methyl-5 α -4-azaandrostan-3-one,
17 β -(4-cyanophenoxy)-4-methyl-5 α -4-azaandrostan-3-one,
17 β -(4-carboxamidophenoxy)-4-methyl-5 α -4-azaandrostan-3-one,
17 β -methylenedioxy-[N-cyclohexyl-N-(N-cyclohexyl-carbamoyl)-
10 carbamoyl]-4-methyl-5 α -4-azaandrostan-3-one,
4-methyl-17 β -(3-pyridyl)oxy-5 α -4-azaandrostan-3-one,
4-methyl-17 β -(2-pyridyl)methoxy-5 α -4-azaandrostan-3-one,
17 β -benzyloxy-4-methyl-5 α -4-azaandrostan-3-one,
15 ethyl 5 α -4-azaandrostan-3-on-17 β -yloxyacetate,
5 α -4-azaandrostan-3-on-17 β -yloxyacetic acid,
5 α -4-azaandrostan-3-on-17 β -yloxy-N-phenylacetamide,
5 α -4-azaandrostan-3-on-17 β -yloxy-N-(4-
20 acetylphenyl)acetamide, diphenylmethyl 5 α -4-azaandrostan-
3-on-17 β -yloxyacetate,
17 β -methylenedioxy-[N-cyclohexyl-N-(N-cyclohexyl-
carbamoyl)carbamoyl]-5 α -4-azaandrostan-3-one,
5 α -4-azaandrostan-3-on-17 β -yloxy-N-[4-(1(RS)-hydroxy-
ethyl)phenyl]acetamide,
25 5 α -4-azaandrostan-3-on-17 β -yloxy-N-(4-t-butyl-
phenyl)acetamide,
17 β -methylenedioxy-[N-isopropyl-N-(N-isopropyl-carbamoyl)-
carbamoyl]-5 α -4-azaandrostan-3-one,
17-(4-methylpentyl)oxy-4-methyl-5 α -4-azaandrostan-3-one,
30 17-hexyloxy-4-methyl-5 α -4-azaandrostan-3-one, 4-methyl-17-
propyloxy-5 α -4-azaandrostan-3-one,
4-methyl-17-undecyloxy-5 α -4-azaandrostan-3-one,
17-allyloxy-4-methyl-5 α -4-azaandrostan-3-one,
17-allyloxy-4-methyl-4-azaandrost-5-en-3-one, or

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17-hexyloxy-4-methyl-4-azaandrost-5-en-3-one.

Novel compounds of this invention further include, but are not limited to:

- 5 17-(4-(isobutyl)benzyloxy)methyl-4-methyl-5 α -4-azaandrostan-3-one,
17-(4-acetamidobenzyloxy)methyl-4-methyl-5 α -4-azaandrostan-3-one,
4-methyl-17-(3-nitrobenzyloxy)methyl-5 α -4-azaandrostan-3-one,
10 4-methyl-17-(phenoxyethoxymethyl)-5 α -4-azaandrostan-3-one,
17-(3-(isopropylthio)propyloxy)methyl-4-methyl-5 α -4-azaandrostan-3-one,
17-(2-fluorobenzyloxy)methyl-4-methyl-5 α -4-azaandrostan-3-one,
4-methyl-17-(3-(trifluoromethyl)benzyloxy)methyl-5 α -4-
15 azaandrostan-3-one,
17-(4-dimethylaminobenzyloxy)methyl-4-methyl-5 α -4-azaandrostan-3-one,
17-((N-t-butyl-carboxamido)methoxymethyl)-4-methyl-5 α -4-
20 azaandrostan-3-one,
20-(3-(ethylthio)propyl)-4-methyl-5 α -4-azapregnan-3-one,
20-(2-(benzyloxy)ethyl)-4-methyl-5 α -4-azapregnan-3-one,
20-(3-methoxybenzyloxy)methyl-4-methyl-5 α -4-azapregnan-3-one,
25 17a-(carboethoxymethoxy)benzyl-4-methyl-5 α -4-azaandrostan-3-one,
20-(4-(methylthio)benzyloxy)methyl-4-methyl-5 α -4-azapregnan-3-one,
4-methyl-17-n-octylthiomethyl-5 α -4-azaandrostan-3-one,
20-(t-butylthiomethyl)-4-methyl-5 α -4-azapregnan-3-one,
30 17-(2-furfuryl)thiomethyl-4-methyl-5 α -4-azaandrostan-3-one,
17-(geranyloxymethyl)-4-methyl-5 α -4-azaandrostan-3-one,
4-methyl-20-(2-(n-nonylthio)ethyl)-5 α -4-azapregnan-3-one,
20-(methylthiomethyl)-4-methyl-5 α -4-azapregnan-3-one,

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17-(4-(benzyloxy)benzyloxy)methyl-4-methyl-5 α -4-azaandrostan-3-one,
20-(diphenylmethylthio)methyl-4-methyl-5 α -4-azapregnan-3-one,
17-(3-(ethylthio)propyl)-4-methyl-5 α -4-azaandrostan-3-one,
5 4-methyl-20-(phenylthiomethyl)-5 α -4-azapregnan-3-one,
17-(ethylsulfonylmethyl)-4-methyl-5 α -4-azaandrostan-3-one, or
17-(4-ethoxybenzyloxy)methyl-4-methyl-5 α -4-azaandrostan-3-one.

10 Also included within the scope of this invention are pharmaceutically acceptable salts or esters, where a basic or acidic group is present in a compound of formula I, such as on the substituted alkyl, cycloalkyl, aryl or heterocyclic moiety. When an
15 acidic substituent is present, i.e. -COOH, there can be formed the ammonium, sodium, potassium, calcium salt, and the like, for use as the dosage form.

Where a basic group is present, i.e. amino, acidic salts, i.e. hydrochloride, hydrobromide, acetate, pamoate, and the like, can
20 be used as the dosage form.

Also, in the case of the -COOH group being present, pharmaceutically acceptable esters can be employed, e.g. acetate, maleate, pivaloyloxymethyl, and the like, and those esters known in
25 the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

The compounds of the present invention, may have asymmetric centers and occur as racemates, racemic mixtures and as individual diastereomers, with all isomeric forms being included in
the present invention.

30 When any variable (e.g., aryl, heterocycle, R¹, R², n, X, etc.) occurs more than one time in any constituent or general structural formula its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

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As used herein "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms (Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl); "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Cycloalkyl" is intended to include saturated mono-, bi- and tricyclic ring groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl (Cyh), cycloheptyl, norbornanyl and adamantyl. "Alkenyl" is intended to include hydrocarbon groups of either a straight or branched configuration with one or more carbon-carbon double bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, and the like. "Halo", as used herein, means fluoro, chloro, bromo and iodo.

As used herein, with exceptions as noted, "aryl" is intended to mean phenyl (Ph) or naphthyl.

The term heterocycle or heterocyclic, as used herein except where noted, represents a stable 5- to 7-membered monocyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidinyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazoliny, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranlyl,

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benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl,
tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl,
thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl.
Morpholino is the same as morpholinyl. Preferred heterocycles are
5 piperidinyl, 2-oxopyrrolodiny, pyrrolyl, pyrazolyl, imidazolyl,
pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl,
morpholinyl, thiazolyl, isothiazolyl, quinuclidinyl, indolyl,
quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl,
10 benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, thienyl, and
benzothienyl.

As used herein, "heteroaryl" represents a stable 5- to 7-
membered monocyclic unsaturated heterocyclic ring, which consists
of carbon atoms and from one to three heteroatoms selected from the
group consisting of N, O and S, and wherein the nitrogen and sulfur
15 heteroatoms may optionally be oxidized, and the nitrogen heteroatom
may optionally be quaternized.

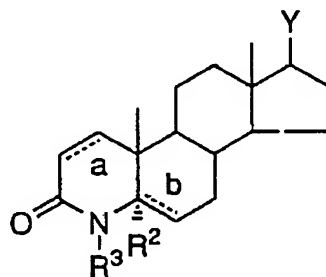
Further abbreviations that may appear herein are
defined as follows:

20	DCC	N,N'-dicyclohexylcarbodiimide
	DIC	1,3-diisopropylcarbodiimide
	DEAD	diethyl azodicarboxylate
	DMAP	4-dimethylaminopyridine
25	DMF	N, N-dimethylformamide
	DMSO	dimethyl sulfoxide
	EtOAc	ethyl acetate
	Ph ₃ P	triphenylphosphine
	m.p (or mp)	melting point
30	THF	tetrahydrofuran
	m.w. (or mw)	molecular weight

Additional methods of making the compounds of the
present invention are made by methods as described as follows and in
general flowsheets IV through VII, below.

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The compounds of this invention can be made from a steroid alcohol starting material, represented by general structural formula VIII:



VIII

wherein a and b are both single bonds and R^2 is hydrogen, or a is a double bond, b is a single bond and R^2 is hydrogen, or a is a single bond, b is a double bond and R^2 is absent; R^3 is -H, methyl or ethyl; Y is -OH or $-(CHR^1)_n-OH$; R^1 is -H, aryl, or C_{1-3} alkyl unsubstituted or substituted with aryl; and n is 1-10. Methods of making starting alcohols of formula VIII are well known to those skilled in the art, and are described, for example, in the following publications: Rasmusson, G.H., et al., *J. Med. Chem.*, **29**, 2298-2315 (1986); Rasmusson, G.H., et al., *J. Med. Chem.*, **27** 1690-1701 (1984).

Furthermore, the starting 4-azasteroid-20-alcohols of formula VIII may be made by several methods well known to those skilled in the art. For example, 4-azasteroids containing a 17-carbonyl group (e.g. carboxaldehyde) may be reacted with the appropriate organo-metallic reagent to yield the corresponding secondary alcohol, while reduction yields the primary alcohol. Also, an appropriate 17-ketone may be reduced (e.g. with sodium borohydride) to the desired alcohol. The above mentioned ketones may be made by several methods well known in the art; one particularly useful method is that of A. Bhattacharya et al., *Synthetic Communications* **20** (17), 2683-2690 (1990), in which an activated

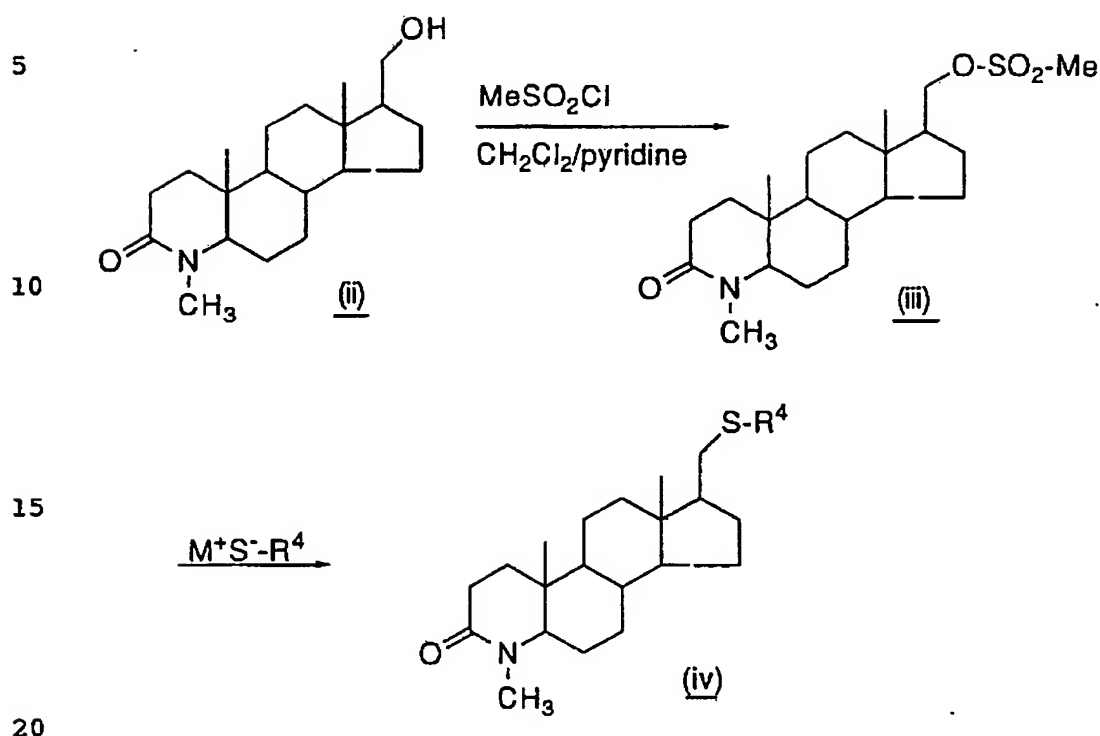
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carbonyl compound is reacted with a suitable Grignard reagent to give the desired ketone. Other activated carbonyl compounds (e.g. pyridine thioesters) may also be used. These alcohol functions may be constructed both before and after the formation of the 4-aza moiety.

For purposes of illustration, general flowsheets IV through VII below employ specific steroid alcohol starting materials such as 17-hydroxymethyl-4-methyl-5 α -4-azaandrostan-3-one (compound (ii) below) or 17-hydroxy-4-methyl-5 α -4-azaandrostan-3-one (compound (v) below) as the starting alcohol. However, the present invention and the synthetic methods described herein are not limited by the use of any particular compounds in any of the schemes or synthetic descriptions presented below, except where otherwise noted, but rather the schemes and synthetic descriptions are presented for illustrative purposes to those skilled in the art. A person skilled in the art would be able to choose the appropriate alcohol starting material to use in the following general synthetic route descriptions to arrive at a target product within the scope of generic formula I.

As depicted in general flowsheet IV below, thioethers (iv) can generally be made by forming the mesylate (iii) of alcohol (ii) by common methods known in the art, e.g. using methanesulfonyl chloride in CH₂Cl₂ with pyridine, and then treating the mesylate with M⁺S⁻-R⁴, wherein M⁺ is a metal ion, e.g. Na⁺ or K⁺, and R⁴ is as defined in formula I. The M⁺S⁻-R⁴ reagents are either commercially available, such as sodium thioethoxide or potassium thiophenoxide, or can be generated by methods well known in the art, e.g., as described in J.Org. Chem., 40, p 1181 (1975) or J. Chem. Soc., p 3127 (1928).

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FLWSHEET IV

As depicted in general flowsheet V, below, the starting alcohol (v) can be treated with a diazo-reagent (vi) using techniques well known in the art, e.g. using boron trifluoride etherate or $\text{Rh}_2(\text{OAc})_4$, to obtain ethers of formula (vii). Diazo-reagents, such as diazomethane, diphenyldiazomethane, benzyldiazo-acetate, etc., are generated by methods well known in the art, such as by the methods described in the following publications: British Patent 1,533,381; British Patent 1,459,285; J. Chem. Soc., Perkins I, p. 2030 (1975); Organic Synthesis, Collective Vol. III, p. 351 (1955); J. Org. Chem., 24, p. 560 (1959).

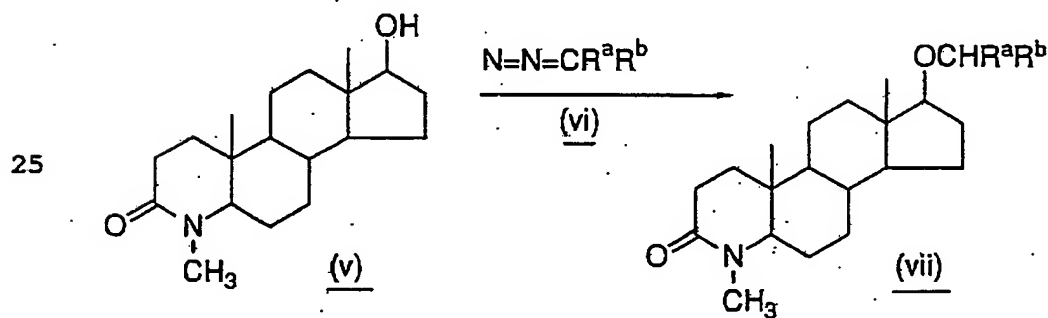
When R^a is $-\text{H}$ and R^b is $-\text{COOC}_2\text{H}_5$ in compound (vii), hydrolysis of the ester with base followed by treatment with acid

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produces compound (viii). The acid (viii) can be coupled with an amine, e.g. an arylamine such as aniline, 4-t-butyl aniline, or p-amino-acetophenone, by common amide coupling procedures well known in the art, e.g., using the carbodiimide method with reagents such as DCC or DIC in the presence of DMAP, to form an amide exemplified by (x). When DCC is used, the sideproduct (xi) is formed as well; when DIC is used, a sideproduct similar to (xi) is formed except instead of a cyclohexyl urea moiety, it contains an isopropyl urea moiety. Treatment of (viii) with a diazo reagent, such as diphenyl diazomethane, and $\text{Rh}_2(\text{Ac})_4$ under conditions well known in the art leads to formation of compounds exemplified by (ix).

The 5α -4-azandrostan-3-on-17-yloxyacetic acid and ethyl 5α -4-azaandrostan-3-on-17B-yloxy-acetate analogs can be prepared according to general scheme 2 but are more preferably prepared according to the routes described in Examples 17 and 21 herein.

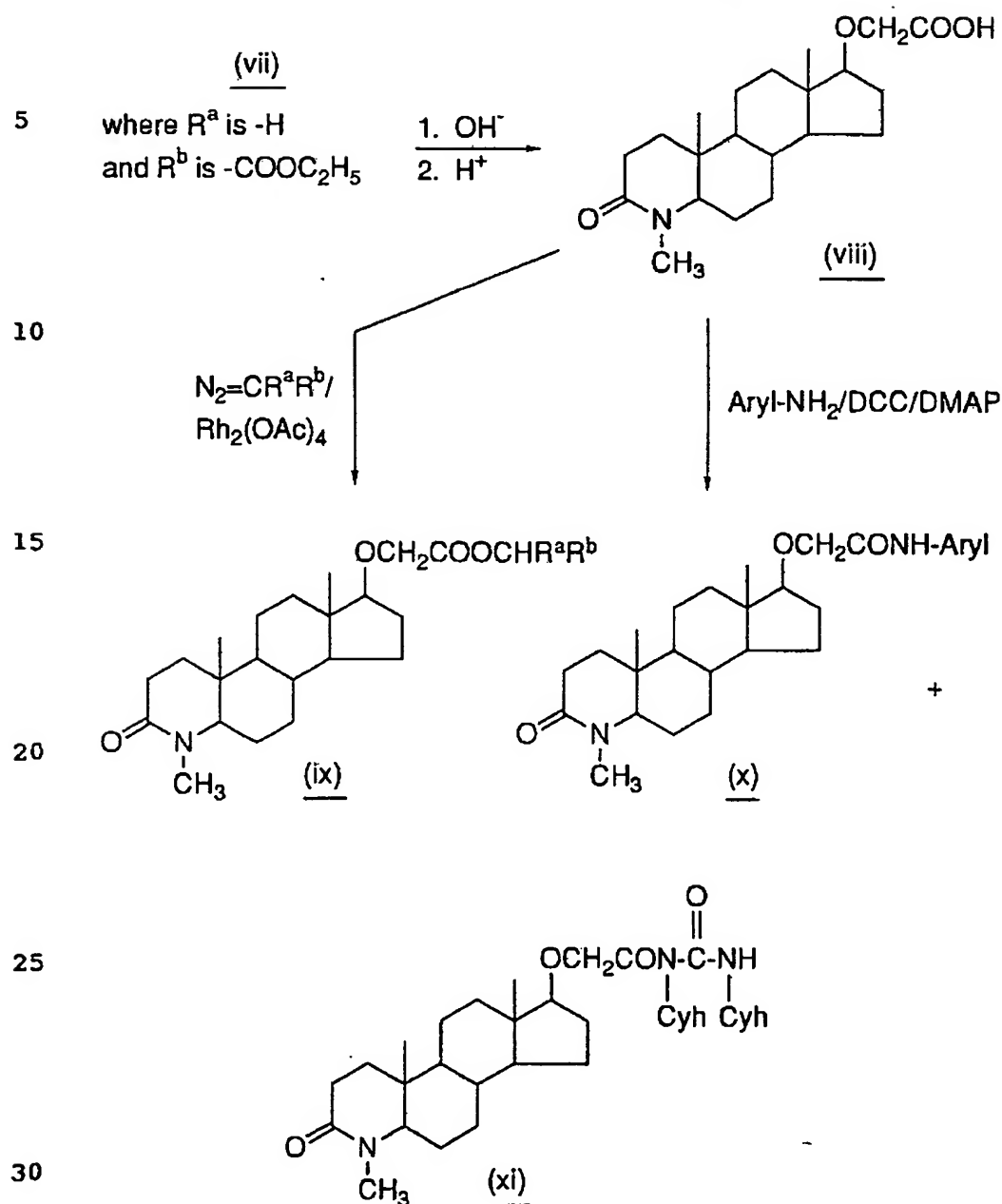
GENERAL FLOWSHEET V


 $\text{R}^a = \text{R}^b = -\text{H};$
 $\text{R}^a = \text{R}^b = -\text{Ph};$ or

 $\text{R}^a = \text{H}$ and $\text{R}^b = -\text{COOC}_2\text{H}_5$ or

 COOCHPh_2

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FLWSHEET V (CONT'D)

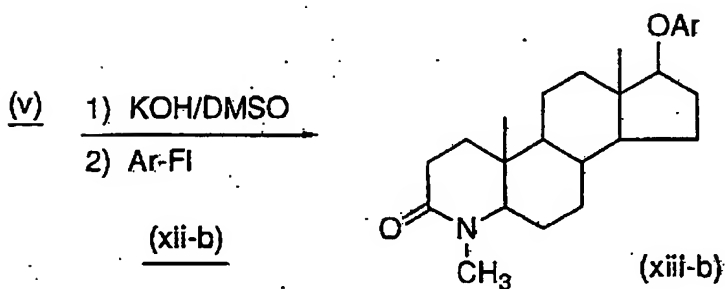
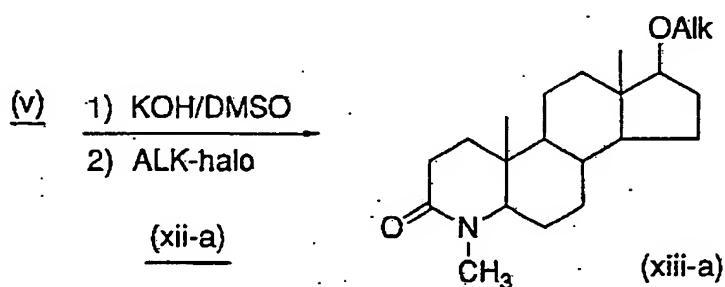
Amide compounds of formula (x) can also be made by alternative methods well known in the art, e.g., by reacting (vii) wherein R^a is -H and R^b is $-\text{COOC}_2\text{H}_5$ directly with an unsubstituted

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or substituted aryl-NH₂ compound and heating the reaction, e.g., to about 170°C - 180°C. Another method, e.g., is to form a mixed anhydride of acid (viii) and react it with the desired primary amine to obtain compounds of formula (x).

As depicted in Scheme 3, below, the starting alcohol (v) can be treated with a strong base, such as NaH or KOH, in an appropriate solvent such as DMF or DMSO, followed by treatment with an alkyl- or alkenyl-halide (xii-a), such as hexyliodide or allylbromide for example, to form the corresponding alkyl- or alkenyl-ether product (xiii-a). Use of KOH in DMSO is preferred.

FLWSHEET VI



Also as depicted in flowsheet V, aryl ether and heteroaryl ether products (xiii-b) can be prepared by treating the steroid alcohol starting material with a fluoroaryl or fluoroheteroaryl compound (xii-b), such as p-nitrofluorobenzene, p-cyanofluoro-benzene or 3-fluoropyridine for example, and NaH or

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KOH in an appropriate solvent such as DMF or DMSO, with KOH/DMF and KOH/DMSO being preferred.

Alternatively, aryl ether and heteroaryl ether products of formula (xiii-b) can be prepared by treating the steroid alcohol starting material with an unsubstituted or substituted hydroxy aryl or hydroxy heteroaryl compound such as phenol or 4-hydroxybiphenyl for example, and triphenylphosphine and diethyl azodicarboxylate (DEAD). With this method, the ether product will have stereochemistry at the 17-position that is the opposite of the starting alcohol when Y is -OH in formula (i). For example, using this procedure, 4-methyl-17 α -phenoxy-5 α -4-azaandrostan-3-one is the product of 17 β -hydroxy-4-methyl-5 α -4-azaandrostan-3-one and phenol.

Heteroaryl ether products can be reduced by methods well known in the art, e.g., by hydrogenation in an appropriate solvent such as MeOH, in the presence of a catalyst such as palladium or platinum on carbon, to obtain compounds of formula I wherein R⁴ is a saturated heterocycle.

As depicted in flowsheet VII below, compounds of formula (xvii) can be prepared by treating the amino hydrochloride derivative (xv) with the appropriate anhydride reagent using methods well known to those skilled in the art. "R^d" in Scheme 4 can be heterocycle, "A" as defined in the generic description of compounds of formula I, or -(CH₂)_q-CO-Q, wherein the variables "q" and "Q" are as defined in the generic description of compounds of formula I. Alternatively, compounds of formula (xvii) where R^d is -(CH₂)_q-CO-Q can be made by treating (xv)

with an anhydride of formula $(\text{CH}_2)_q \begin{matrix} \text{CO} \\ \diagup \quad \diagdown \\ \text{O} \end{matrix}$ and base,

such as pyridine, to make intermediate compounds of formula (xvii) where R^d is -(CH₂)_q-COOH, and then making amides and esters

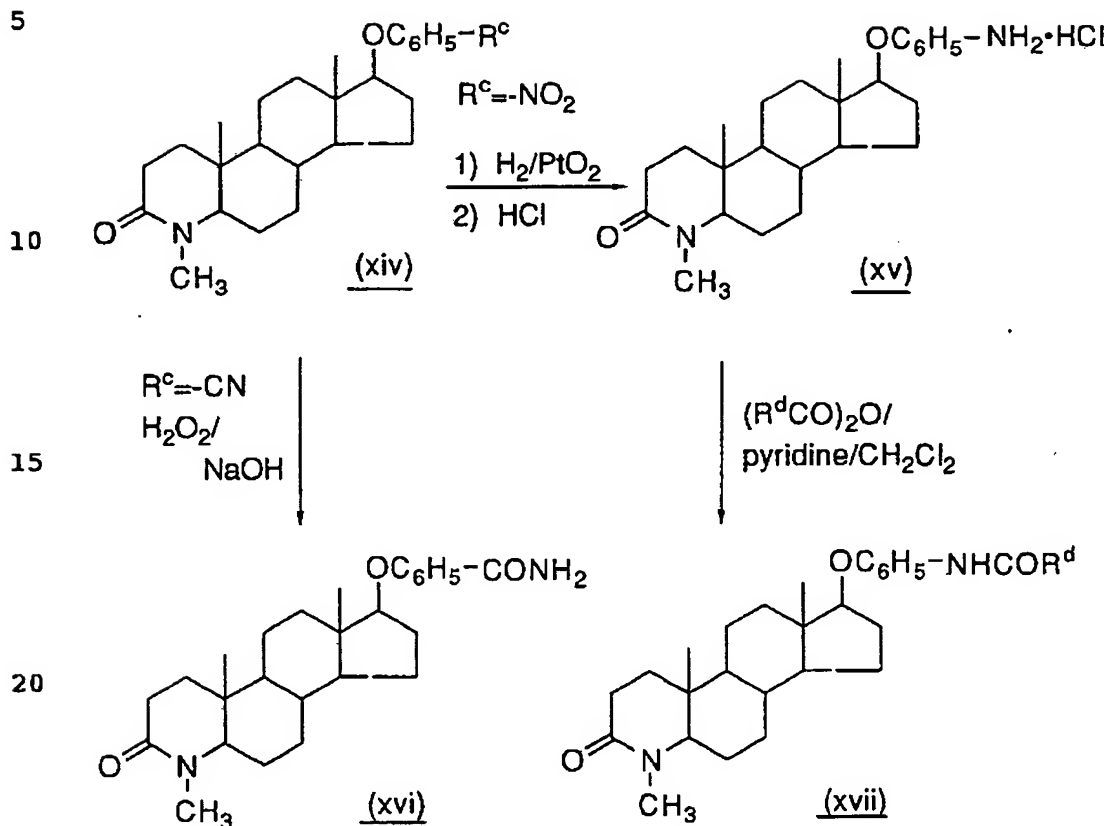
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from the intermediate acid. Compound (xv) is prepared by reduction of the nitro group of compound (xiv) wherein R^C is $-NO_2$, by common techniques well known in the art, e.g., hydrogenation in the presence of a catalyst such as PtO_2 , and treatment with an acid such as HCl. Compound (xiv) wherein R^C is $-NO_2$ can be prepared by methods described above for making aryl ethers.

Also as depicted in scheme 4, below, the cyano group of compound (xiv), wherein R^C is $-CN$, can be hydrolyzed by methods well known in the art, e.g., by treatment with H_2O_2 and base such as NaOH, to provide compound (xvi). The primary amide of (xvi) can be alkylated by methods well known in the art, such as with methyl iodide, for example, to make the secondary or tertiary amide derivatives.

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FLOWSHEET VII



By using methods well known to those skilled in the art, the diazonium salt of compound (xv) can be made by treatment of (xv) with HNO_2 or an alkyl nitrite. The resulting diazonium salt can be used as an intermediate in a variety of reactions to replace the diazonium moiety to make other substituted aryl ether derivatives. For example, the diazonium salt moiety can be replaced with a halo, -CN, -OH or alkoxy group by common methods well known to those skilled in the art. Or the diazonium moiety can be replaced with hydrogen to yield the unsubstituted aryl ether derivative.

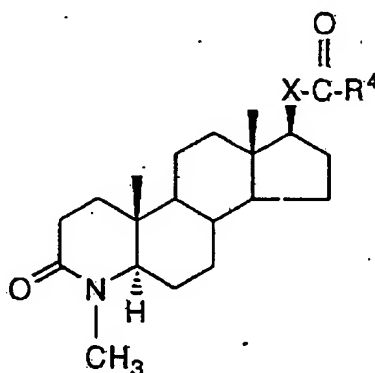
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Alternatively, the ethers of this invention may be obtained by first preparing the desired ether and thioether groups at the desired position in the appropriate non-aza steroid followed by ring opening of the A-ring and subsequent closure to the desired 4-azasteroid. For example, a 20-alkoxy-substituted pregn-4-en-3-one may be oxidized with permanganate periodate to the corresponding seco-acid which is then reacted with an appropriate amine to give, after reduction of the first obtained 4-aza-5-enesteroid, the desired 20-ether-substituted-5 α -4-azapregnan-3-one.

EXAMPLES FOR THE CASE WHEN SUBSTITUENT "A" OF GENERAL FORMULA "I" IS AS DEFINED IN GROUP "III(A)"

DESCRIPTION WHERE STRUCTURE A IS IIIA

A first preferred embodiment of this class is represented by compounds of formula IX:



IX

wherein R⁴ is -C₁₋₂₀alkyl, unsubstituted or substituted with one or more of

-OH, halo, -C₁₋₈alkoxy, -C₁₋₆alkenyl, -S(O)_p-R⁵, -N(R⁵)₂, aryl unsubstituted or substituted with one or more of aryl, R⁷ or R⁹, heterocycle unsubstituted or substituted with one or

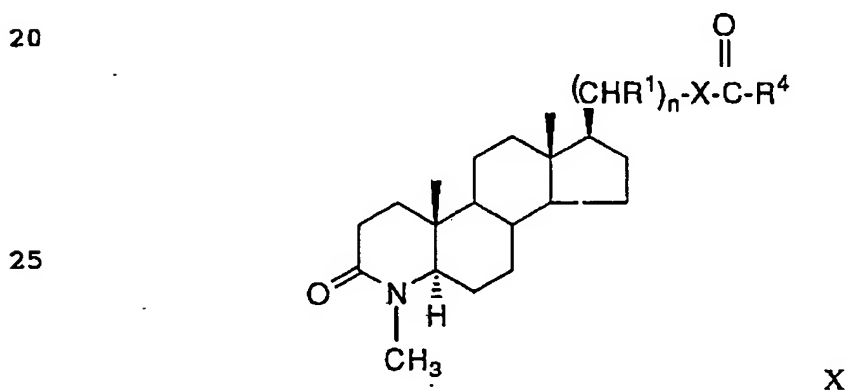
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more of R^7 or R^9 , or $-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9 , and X , p , R^5 , R^7 , and R^9 are all as defined in formula I.

5 Another preferred embodiment of this invention is represented by compounds of general structural formula IX wherein R^4 is $-C_{1-20}$ alkyl substituted with $-\text{CONR}^5R^5$, $-\text{COOR}^6$ or $-\text{CONR}^8\text{CONHR}^8$, and X , R^5 , R^6 , and R^8 are all as defined in formula I.

10 Another preferred embodiment of this invention is represented by compounds of formula IX wherein R^4 is aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9 ; heterocycle unsubstituted or substituted with one or more of R^7 or R^9 ; $-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9 ; $-\text{NR}^5R^5$; or $-\text{OR}^5$;
15 and X , R^5 , R^7 , and R^9 are all as defined in formula I.

Another preferred embodiment of this invention is represented by compounds of general structural formula X:



30

wherein R^4 is $-C_{1-20}$ alkyl, unsubstituted or substituted with one or more of

$-\text{OH}$, halo, $-C_{1-8}$ alkoxy, $-C_{1-6}$ alkenyl, $-\text{S(O)}_p-R^5$, $-\text{N(R}^5)_2$, aryl unsubstituted or substituted with one or more of aryl, R^7

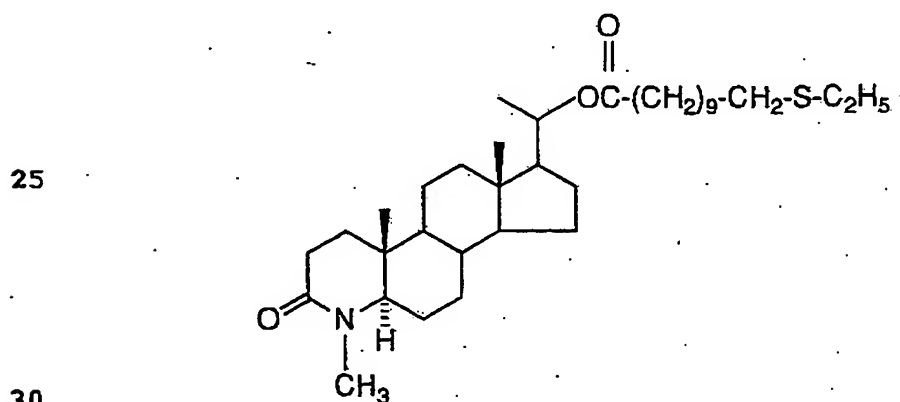
- 98 -

or R⁹, heterocycle unsubstituted or substituted with one or more of R⁷ or R⁹, or -C₃₋₁₀ cycloalkyl unsubstituted or substituted with one or more of R⁷ or R⁹,
 5 and X, n, p, R¹, R⁵, R⁷, and R⁹ are all as defined in formula I.

Another preferred embodiment of this invention is represented by compounds of general structural formula X wherein R⁴ is -C₁₋₂₀ alkyl substituted with -CONR⁵R⁵, -COOR⁶ or
 10 -CONR⁸CONHR⁸,
 and X, n, R¹, R⁵, R⁶, and R⁸ are all as defined in formula I.

Another preferred embodiment of this invention is represented by compounds of formula X wherein R⁴ is aryl unsubstituted or substituted with one or more of aryl, R⁷ or
 15 R⁹; heterocycle unsubstituted or substituted with one or more of R⁷ or R⁹; -C₃₋₁₀ cycloalkyl unsubstituted or substituted with one or more of R⁷ or R⁹; -NR⁵R⁵; or -OR⁵;
 and X, n, R¹, R⁵, R⁷, and R⁹ are all as defined in formula I.

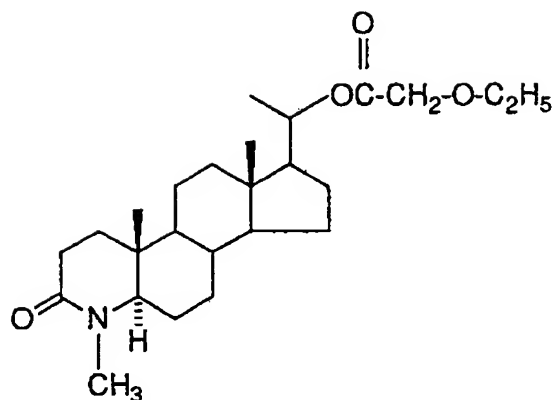
Novel compounds of the present invention include but
 20 are not limited to the following compounds:



20-(11-(ethylthio)undecanoyloxy)-4-methyl-5α-4-azapregnan-3-one,

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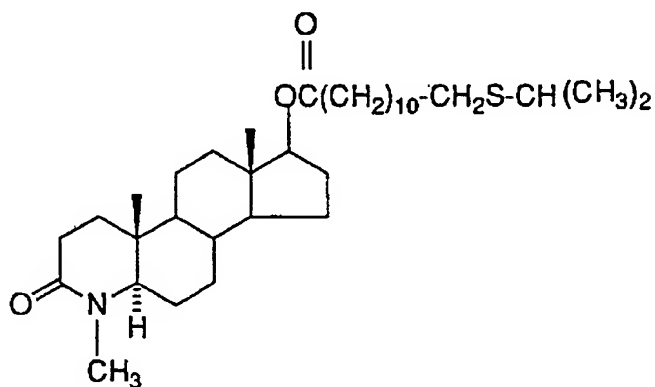
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10

20-ethoxyacetyloxy-4-methyl-5α-4-azapregnan-3-one,

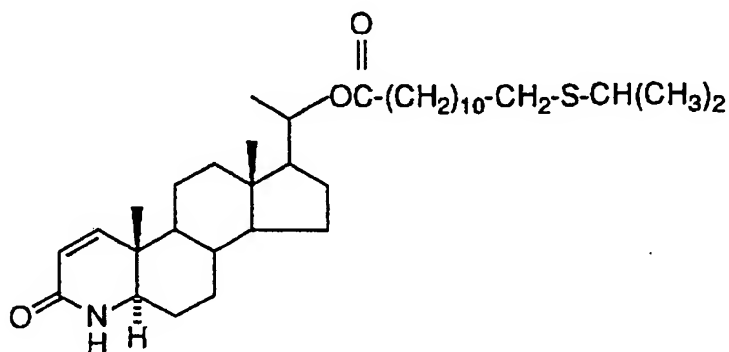
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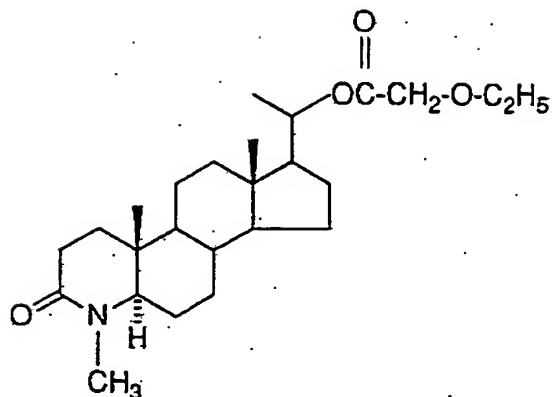
17-(12-(isopropylthio)dodecanoyloxy)-4-methyl-5α-4-azaandrostan-
25 3-one,

30



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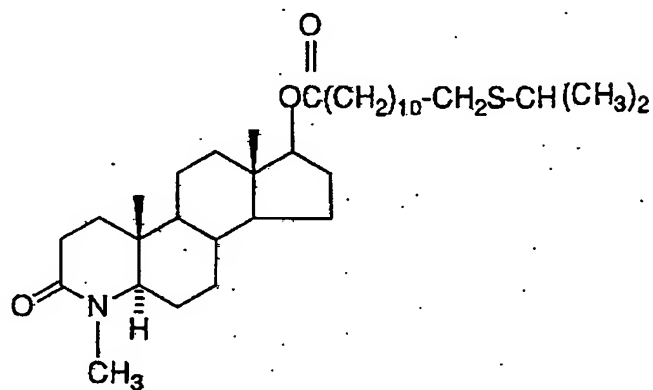
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10

20-ethoxyacetyloxy-4-methyl-5 α -4-azapregnan-3-one,

15

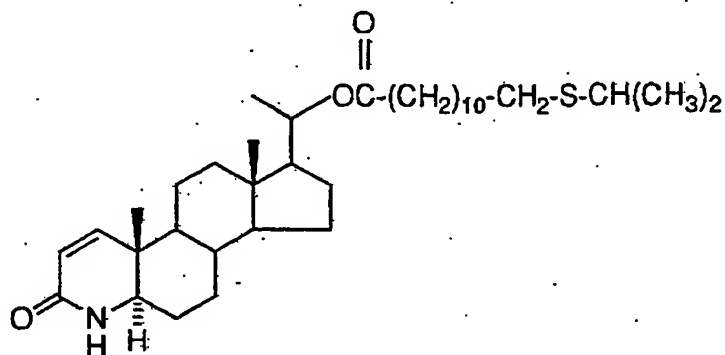


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25

17-(12-(isopropylthio)dodecanoyloxy)-4-methyl-5 α -4-azaandrost-3-one,

30



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- 20-(12-(isopropylthio)dodecanoyloxy)-4-methyl-5 α -4-
azapregnan-3-one,
20-(11-(ethylsulfinyl)undecanoyloxy)-4-methyl-5 α -4-azapregnan-
3-one,
5 20-(12-(t-butylthio)dodecanoyloxy)-4-methyl-5 α -4-aza-pregnan-
3-one
4-methyl-20-(4-thien-2-yl)butyroyloxy-5 α -4-aza-pregnan-3-one,
20-trimethylacetyloxy-5 α -4-azapregnan-3-one,
10 20-(9-(isopropylthio)nonanoyloxy)-5 α -4-azapregnan-3-one,
20-(12-(isopropylthio)dodecanoyloxy)-5 α -4-azapregnan-3-one,
20-acetoxymethyl-4-methyl-5 α -4-azapregnan-3-one,
4-methyl-20-(trimethylacetyloxy)methyl-5 α -4-aza-pregnan-3-
one,
15 20-(12-(isopropylthio)dodecanoyloxy)methyl-4-methyl-5 α -4-
azapregnan-3-one,
17-acetyloxymethyl-4-methyl-5 α -4-azaandrostan-3-one,
4-methyl-17-trimethylacetyloxymethyl-5 α -4-azaandrostan-3-one,
17-(2-ethylhexanoyloxy)methyl-4-methyl-5 α -4-azaandrostan-3-
one,
20 17-(methylaminocarbonyloxymethyl)-4-methyl-5 α -4-
azaandrostan-3-one,
17-(12-(isopropylthio)dodecanoyloxy)methyl-4-methyl-5 α -4-
azaandrostan-3-one,
17 β -(benzylaminocarbonyloxy)-4-methyl-5 α -4-azaandrostan-3-
one,
25 20-trimethylacetyloxy-5 α -4-azapregn-1-ene-3-one, or
20-(t-butylaminocarbonyloxy)-4-methyl-5 α -4-azapregnan-3-one.

- 30 Novel compounds of the present invention further
include, but are not limited to the following compounds:
17-(2-furylacetoxymethyl)-4-methyl-5 α -4-azaandrostan-3-one,
17-(4-isopropylphenylacetoxymethyl)-4-methyl-5 α -4-
azaandrostan-3-one,

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- 17-(cyclohexylacetoxymethyl)-4-methyl-5 α -4-azaandrostane-3-one,
17-(3-indolylacetoxymethyl)-4-methyl-5 α -4-azaandrostane-3-one,
17-(4-methylcyclohexanecarbonyloxymethyl)-4-methyl-5 α -4-
5 azaandrostane-3-one,
17-(4-(3-indolyl)-butyroyloxymethyl)-4-methyl-5 α -4-
azaandrostane-3-one,
17-(4-isobutylbenzoyloxymethyl)-4-methyl-5 α -4-azaandrostane-3-
one,
10 17-(acetoxycetyloxymethyl)-4-methyl-5 α -4-azaandrostane-3-one,
17-(6-bromohexanoyloxymethyl)-4-methyl-5 α -4-azaandrostane-3-
one,
4-methyl-20-(4-nitrobenzoyloxymethyl)-5 α -4-azapregnan-3-one,
20-((3-acetamido)benzoyloxy)-4-methyl-5 α -4-azapregnan-3-one,
15 20-(3,4-dimethoxyphenylacetyloxymethyl)-4-methyl-5 α -4-
azapregnan-3-one,
17-(4-ethoxybenzoyloxymethyl)-4-methyl-5 α -4-azaandrostane-3-
one,
4-methyl-20-(palmitoyloxymethyl)-5 α -4-azapregnan-3-one,
20 17-(iminodibenzyl-5-carbonyloxymethyl)-4-methyl-5 α -4-
azaandrostane-3-one,
4-methyl-20-(stearoyloxy)-5 α -4-azapregnan-3-one,
17-(3,5-bis-(trifluoromethyl)benzoyloxymethyl)-4-methyl-5 α -4-
azaandrostane-3-one,
25 17-(3-cyanobenzoyloxymethyl)-4-methyl-5 α -4-azaandrostane-3-
one,
20-(heptafluorobutyroyloxymethyl)-4-methyl-5 α -4-azapregnan-
3-one,
20 20-(4-benzoylbenzoyloxymethyl)-4-methyl-5 α -4-azapregnan-3-
one,
17-(benzotriazol-5-carbonyloxymethyl)-4-methyl-5 α -4-
azaandrostane-3-one,
20-(3,5-difluorobenzoyloxy)-4-methyl-5 α -4-azapregnan-3-one,

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17-(bis-(4-isopropyl)phenyl)acetyloxymethyl-4-methyl-5 α -4-
azaandrostan-3-one,
4-methyl-20-(salicyloyloxymethyl)-5 α -4-azapregnan-3-one,
17-((3-hydroxy-4,4,4-trichlorobutyroyloxy)methyl)-4-methyl-
5 α -4-azaandrostan-3-one, or
17-(cinnamoyloxymethyl)-4-methyl-5 α -4-azaandrostan-3-one.

Also included within the scope of this invention are
pharmaceutically acceptable salts or esters, where a basic or acidic
group is present in a compound of formula I, such as on the
substituted alkyl, cycloalkyl, aryl or heterocyclic moiety. When an
acidic substituent is present, i.e. -COOH, there can be formed the
ammonium, sodium, potassium, calcium salt, and the like, for use as
the dosage form.

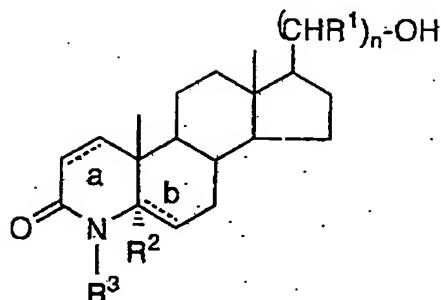
Where a basic group is present, i.e. amino, acidic salts,
i.e. hydrochloride, hydrobromide, acetate, pamoate, and the like, can
be used as the dosage form.

Also, in the case of the -COOH group being present,
pharmaceutically acceptable esters can be employed, e.g. acetate,
maleate, pivaloyloxymethyl, and the like, and those esters known in
the art for modifying solubility or hydrolysis characteristics for use
as sustained release or prodrug formulations.

The compounds of the present invention, may have
asymmetric centers and occur as racemates, racemic mixtures and as
individual diastereomers, with all isomeric forms being included in
the present invention.

The compounds of this invention can alternatively be
made generally from a steroid alcohol starting material, represented
by formula XI:

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XII

wherein a and b are both single bonds and R² is hydrogen, or
a is a double bond, b is a single bond and R² is hydrogen, or
a is a single bond, b is a double bond and R² is absent;
R¹ is -H, aryl, or C₁₋₃alkyl unsubstituted or substituted with aryl;
R³ is -H, methyl or ethyl; and n is zero through 10.

Methods of making starting alcohols of formula XI are well known to those skilled in the art, and are described, for example, in the following publications: Rasmusson, G.H. et al., J. Med. Chem., 29, 2298-2315 (1986); Rasmusson, G.H. et al., J. Med. Chem., 27, 1690-1701 (1984).

Furthermore, the starting 4-azasteroid-20-alcohols of Formula XI may be made by several methods well known to those skilled in the art. For example, 4-azasteroids containing a 17-carbonyl group (e.g. carboxaldehyde) may be reacted with the appropriate organo-metallic reagent to yield the corresponding secondary alcohol, while reduction yields the primary alcohol. Also, an appropriate 17-ketone may be reduced (e.g. with sodium borohydride) to the desired alcohol. The above mentioned ketones may be made by several methods well known in the art; one particularly useful method is that of A. Bhattacharya et al., Synthetic Communications 20(17), 2683-2690 (1990), in which an activated carbonyl compound is reacted with a suitable Grignard reagent to give the desired ketone. Other activated carbonyl compounds (e.g. pyridine thioesters) may also be used.

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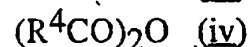
These alcohol functions may be constructed both before and after the formation of the 4-aza moiety.

One method of preparing compounds of formula I is to condense the starting steroid alcohol with an acid of formula (ii)



under conditions known to those skilled in the art, e.g., in an appropriate solvent such as CH_2Cl_2 , in the presence of 4-(dimethylamino)-pyridine (DMAP) and N,N'-dicyclohexylcarbodiimide (DCC).

Another method of preparing compounds of formula I is to combine the starting alcohol (i) with an acid chloride of formula (iii) or acid anhydride or mixed anhydride of formula (iv)



under conditions known to those skilled in the art, e.g. under dry conditions using an appropriate solvent such as CH_2Cl_2 at a reduced temperature, such as about 0°C , in the presence of a base such as pyridine.

Carbamate derivatives of formula I can be prepared by reacting the starting alcohol XI with an isocyanate compound, such as benzyl isocyanate or t-butylisocyanate for example, under conditions known to those skilled in the art, e.g., under dry conditions in an appropriate solvent such as benzene, in the presence of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), with heating e.g. to $60^\circ\text{-}70^\circ\text{C}$.

The thiol esters may be conveniently prepared from the corresponding alcohol via the literature procedure described in Tetrahedron Letters, 22 (1981) pp. 3119-3122, that is, the alcohol and a thiolacid are reacted together in the presence of the preformed adduct from triphenylphosphine and diisopropyl azodicarboxylate.

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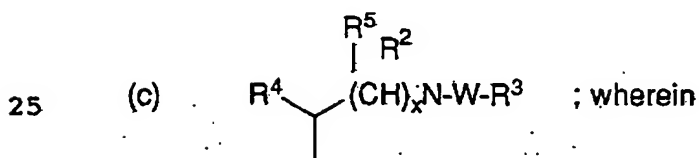
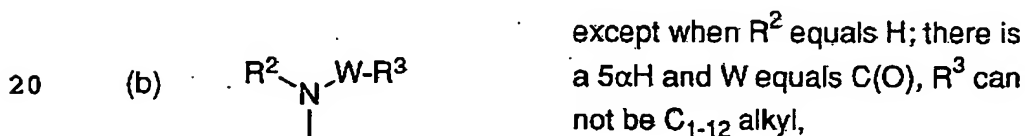
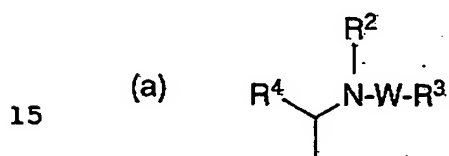
Alternatively, the free thiol obtained from these thiolesters via standard saponification or reduction methods may then be acylated via standard procedures to obtain other thiolesters.

5 The variable "R⁴" used in the above synthetic method descriptions is defined in formula I.

EXAMPLES FOR THE CASE WHEN SUBSTITUENT "A" OF
GENERAL FORMULA "I" IS AS DEFINED IN GROUP "IV(A)"

10 An embodiment of this category is where:

A is:



R¹ is:

30 H, or
C₁₋₂₀ alkyl;

R² is:

H, or
C₁₋₂₀ alkyl;

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R³ is:

- 5 H,
C₁₋₂₀ alkyl,
C₆₋₁₄ aryl,
heteroaryl,
C₆₋₁₄ arylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyl,
10 C₁₋₂₀ alkylthioC₁₋₂₀alkyl,
C₁₋₂₀ alkylsulfonylC₁₋₂₀alkyl,
C₁₋₂₀ alkylsulfinylC₁₋₂₀alkyl,
C₁₋₂₀ alkyloxycarbonylC₁₋₂₀alkyl,
C₁₋₂₀ alkylC₆₋₁₄arylC₁₋₂₀alkyl,
carboxyC₁₋₂₀alkyl,
15 C₁₋₂₀alkyloxyC₁₋₂₀alkyl,
C₁₋₂₀alkoxycarbonylC₁₋₂₀alkyl,
C₁₋₂₀alkylcarbonylC₁₋₂₀alkyl,
C₃₋₂₀cycloalkyl,
C₃₋₂₀cycloalkylC₁₋₂₀alkyl,
20 C₆₋₁₄ arylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyloxycarbonylC₁₋₂₀ alkyl,
haloC₁₋₂₀alkyl,
halohydroxyC₁₋₂₀alkyl,
hydroxyC₁₋₂₀alkyl,
25 thiosulfatoC₁₋₂₀alkyl,
C₆₋₁₄ arylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
diarylC₁₋₂₀alkyl,
triarylC₁₋₂₀alkyl,
30 C₂₋₂₀ alkenyl,
C₂₋₂₀ alkenylC₁₋₂₀alkyl,
C₆₋₁₄ arylC₂₋₂₀alkenyl,
heteroarylC₂₋₂₀alkenyl,
C₆₋₁₄ arylcarbonylarylC₁₋₂₀alkyl,
C₂₋₂₀alkynylC₁₋₂₀alkyl,

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C₆₋₁₄ arylC₂₋₂₀alkynylC₁₋₂₀alkyl, or
heteroarylC₂₋₂₀alkynylC₁₋₂₀alkyl;

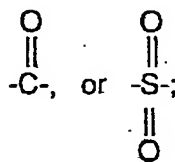
5 R⁴ is

H,
C₁₋₂₀ alkyl,
C₆₋₁₄ aryl, or
heteroaryl;

10 R⁵ is:

H, or
C₁₋₂₀ alkyl;

15 W is



20

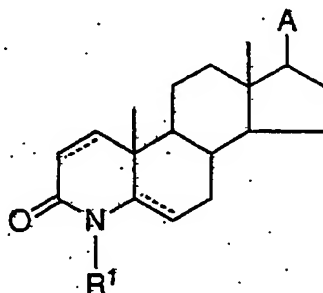
x is an integer from 1 to 25;

and dashes indicate a double bond is optionally present.

25

Advantageously, compounds of the following general
structural formula XII are disclosed:

30

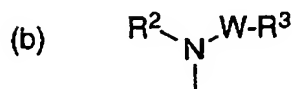
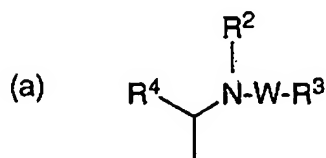


XII

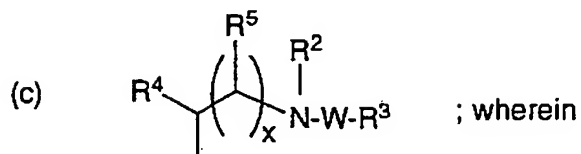
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and the pharmaceutically acceptable salts thereof,
wherein

A is:



except when R^2 equals H; there is
a 5 α H and W equals C(O), R^3 can
not be C₁₋₁₂ alkyl,



R^1 is:

H, methyl or ethyl;

R^2 is:

H, or
C₁₋₂₀alkyl;

R^3 is:

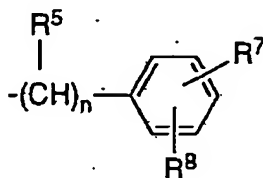
H,
C₁₋₂₀alkyl further comprising a straight or branched chain
alkane of up to 20 carbon atoms;

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C₆₋₁₄ aryl wherein aryl comprises a mono or polycyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R comprises H, C₁₋₆alkyl, arylC₁₋₂₀alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C₁₋₈alkyloxy, carboxy C₀₋₁₀alkyl, or halogen or aryl is directly substituted independently with hydroxyl, haloC₁₋₂₀alkyl, carboamide, benzoyl, C₁₋₂₀alkyloxy, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, cyano, nitro, acetamide or halogen;

heteroaryl which comprises a mono or polycyclic system composed of 5 or 6-membered aromatic rings containing 1, 2, 3 or 4 heteroatoms chosen from N, O, or S and either unsubstituted or substituted with R or independently with hydroxyl C₁₋₂₀alkyloxy, C₁₋₂₀alkyl, benzoyl, carboamide, acetamide, halogens, C₂₋₂₀alkenyl, cyano, nitro, or haloalkyl directly bonded to the aromatic carbon atom(s);

C₆₋₁₄ arylC₁₋₂₀alkyl of the formula:



wherein the aromatic ring is optionally and independently substituted with R⁷ and R⁸ wherein R⁷ and R⁸ comprise:

H,
CH₃,
C₂H₅,
carboxamido,
OCH₃,
C₁C₆alkylthio,
C₁C₆alkylsulfinyl,

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C₁C₆alkylsulfonyl,NH₂,CH₃NH, (CH₃)₂N-,NO₂,

5

CN,

OH,

F,

acetamido,

10

Cl,

OC₂H₅,CF₃,

isopropyl, or

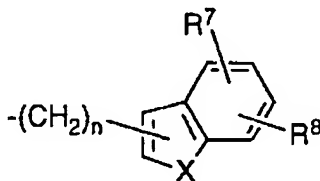
isobutyl; n equals 1-20 and the C₁₋₂₀alkyl group is optionally
15 substituted with R⁷;HeteroarylC₁₋₂₀alkyl further comprising the formula

20



, or

25



wherein X equals O, S, or NR; and n equals 1-20;

30

C₁₋₂₀alkylsulfonylC₁₋₂₀alkylC₁₋₂₀alkylthioC₁₋₂₀alkylC₁₋₂₀alkylsulfinylC₁₋₂₀alkyl comprising the formula:
$$-(CH_2)_nS(O)_p-R^9 \text{ wherein } R^9 \text{ comprises}$$

$$CH_3,$$

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C₂H₅,
 C₃H₇,
 C₄H₉,
 isopropyl,
 5 isobutyl,
 sec-butyl,
 t-butyl,
 isopentyl,
 neopentyl, or
 10 isohexyl; n equals 1-20, p = 0-2;

C₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl further comprising the formula:

15
$$-(\text{CH}_2)_n-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{OR}^{10}$$
 wherein R¹⁰
 comprises:
 CH₃,
 C₂H₅,
 20 C₃H₇,
 C₄H₉, or
 C₅H₁₁; and n equals 1-20;

CarboxylC₁₋₂₀alkyl further comprising:

25
$$-(\text{CH}_2)_n-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{OH}; n = 1-20;$$

C₁₋₂₀alkylcarbonylC₁₋₂₀alkyl further comprising the formula

30
$$-(\text{CH}_2)_n-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}(\text{CH}_2)_m-\text{CH}_3,$$

 n equals 1-20;
 m equals 0-19;

C₃₋₂₀cycloalkylC₁₋₂₀alkyl of the formula:

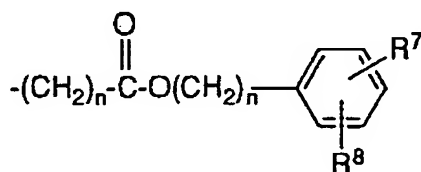
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-(CH₂)_n-(cycloalkyl) wherein the cycloalkyl portion comprises monocyclic, bicyclic, or polycyclic hydrocarbons of up to 20 carbon atoms wherein the rings are optionally substituted with R¹; and n = 1-20;

5

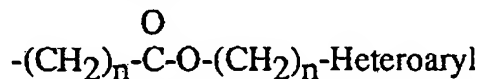
ArylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl of the formula:

10



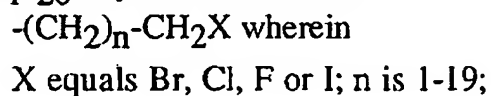
15 wherein n = 1-20;

HeteroarylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl of the formula:

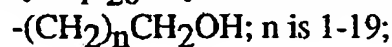


20 wherein Heteroaryl is as defined and n = 1-20;

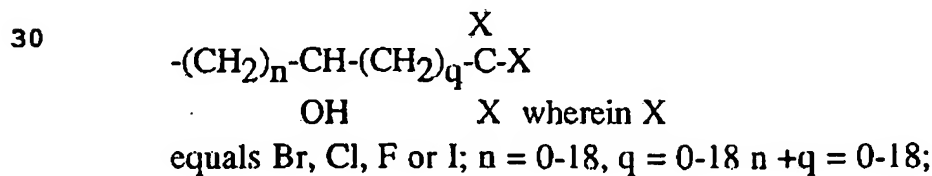
haloC₁₋₂₀alkyl of the formula:



25 hydroxylC₁₋₂₀alkyl of the formula:



halohydroxylC₁₋₂₀alkyl of the formula:

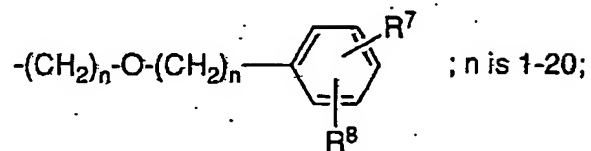


ThiosulfatoC₁₋₂₀alkyl of the formula:

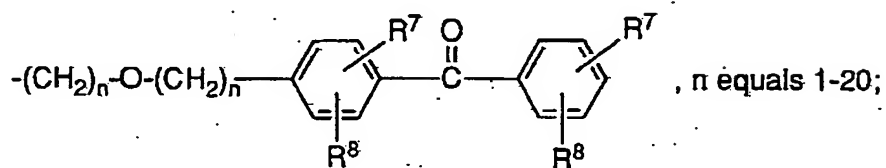
- 114 -

$-(CH_2)_nCH_2SSO_3Na$; n is 1-20;

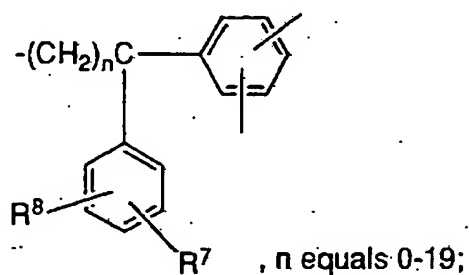
Aryl C_{1-20} alkyloxy C_{1-20} alkyl of the formula:



10 Arylcarbonylaryl C_{1-20} alkyl of the formula:

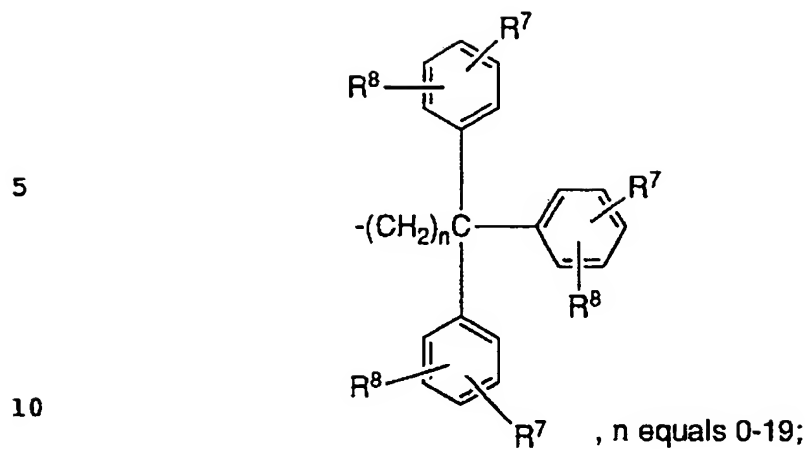


20 Diaryl C_{1-20} alkyl of the formula:

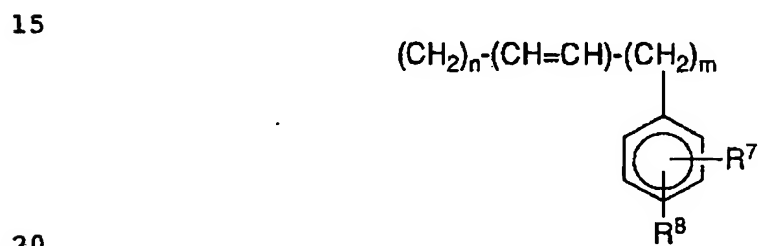


30 Triaryl C_{1-20} alkyl of the formula:

- 115 -



C₆₋₁₄arylC₂₋₂₀alkenyl of the formula:



wherein:

n = 0-18,

m = 0-18,

25 n + m = 0-18;

R⁴ is

H,

C₁₋₂₀alkyl,

C₆₋₁₄aryl, or

30 heteroaryl;

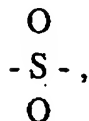
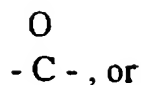
R⁵ is:

H, or

C₁₋₁₂alkyl;

- 116 -

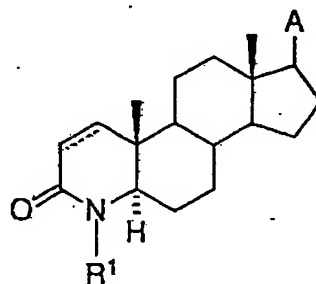
W is:



x is an integer from 1-10;

and the dashes indicate a double bond is optionally present.

Compounds of the general structural formula XIII

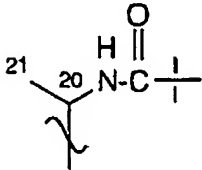
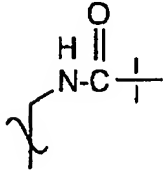
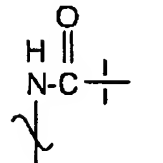
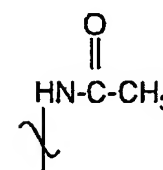


XIII

and listed in Table 1 are representative of the compounds claimed in the instant invention. In a preferred embodiment, R¹ may be H or CH₃ and A may be as indicated in Table 1. Particular representative chemical names are also listed in Table 1 adjacent to the respective side chain and specifically reflect whether the 1 position is saturated or unsaturated. Advantageously, R¹ is CH₃, A is as indicated in Table 1 and the 1 position is saturated.

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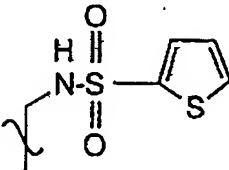
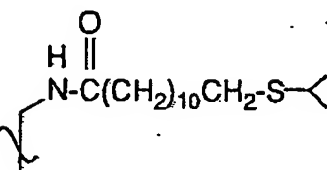
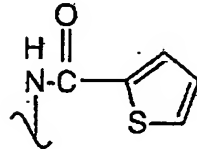
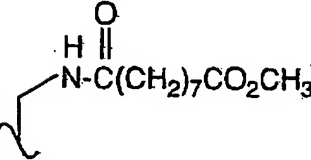
TABLE 1

<u>Side Chain A</u>	<u>Compound(s):</u>
5 (1) 	4-methyl-20(trimethylacetamido)- 5 α -4-aza-pregnan-3-one 4-methyl-20(trimethylacetamido)- 5 α -4-aza-1-pregnen-3-one
10 (2) 	4-methyl-17 β (trimethylacetamidomethyl)-4-aza- 5 α -androst-1-en-3-one 4-methyl-17 β (trimethylacetamidomethyl)-4-aza- 5 α -androstan-3-one
15 (3) 	4-methyl-17 β (trimethylacetamido)-4-aza- 5 α -androst-1-en-3-one 4-methyl-17 β (trimethylacetamido)-4-aza- 5 α -androstan-3-one
20 (4) 	17 β (acetamido)-4-methyl-4-aza- 5 α -androst-1-ene-3-one 17 β (acetamido)-4-methyl-4-aza- 5 α -androstan-3-one

30

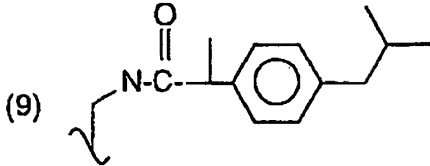
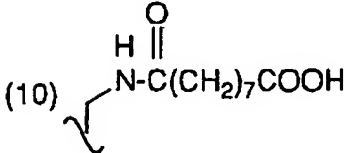
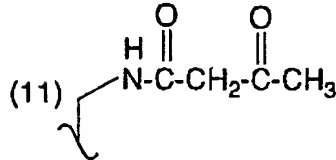
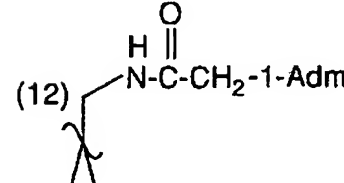
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TABLE 1 (CONT'D)

Side Chain A	Compound(s):
(5) 	4-methyl-17β(2-thiophenesulfonamidomethyl)-4-aza-5α-androst-1-en-3-one 4-methyl-17β(2-thiophenesulfonamidomethyl)-4-aza-5α-androstan-3-one
(6) 	17β(isopropylthiododecanoylamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one 17β(isopropylthiododecanoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one
(7) 	4-methyl-17β(2-thiophenecarboxamidomethyl)-4-aza-5α-androst-1-en-3-one 4-methyl-17β(2-thiophenecarboxamidomethyl)-4-aza-5α-androstan-3-one
(8) 	17β(carbomethoxyoctanoylamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one 17β(carbomethoxyoctanoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one

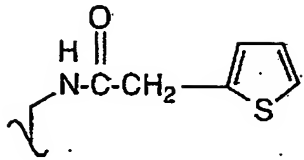
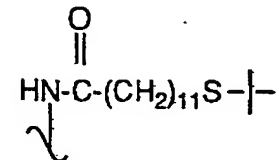
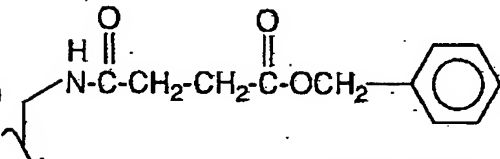
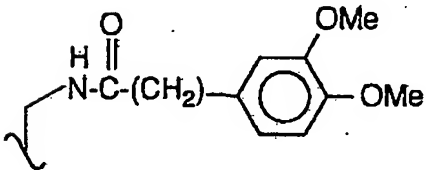
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TABLE 1 (CONT'D)

Side Chain A	Compound(s):
5	
(9) 	17β((2-(4-isobutylphenyl)-propionamido-methyl)-4-methyl-4-aza-5α-androst-1-en-3-one 17β((2-(4-isobutylphenyl)-propionamido-methyl)-4-methyl-4-aza-5α-androstan-3-one
10	
(10) 	17β(8-carboxyoctanoylamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one 17β(8-carboxyoctanoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one
15	
(11) 	17β(acetoacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one 17β(acetoacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one
20	
(12) 	17β(1-Adamantylacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one 17β(1-Adamantylacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one
25	
30	

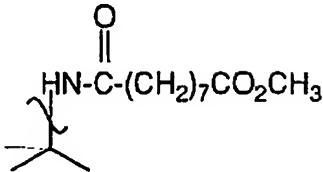
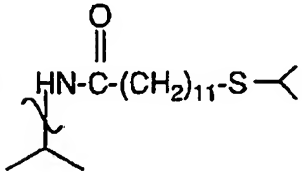
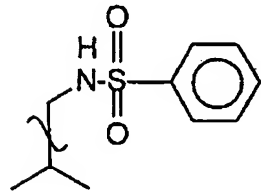
- 120 -

TABLE 1 (CONT'D)

Side Chain A	Compound(s):
5 (13) 	4-methyl-17β(2-thiopheneacetamidomethyl)- 4-aza-5α-androst-1-en-3-one 4-methyl-17β(2-thiopheneacetamidomethyl)- 4-aza-5α-androstan-3-one
10 (14) 	17β(12-(t-butylthio)dodecanoylamido)- 4-methyl-4-aza-5α-androst-1-en-3-one 17β(12-(t-butylthio)dodecanoylamido)- 4-methyl-4-aza-5α-androstan-3-one
15 (15) 	17β(3-(carbobenzyloxy)propionamidomethyl)- 4-methyl-4-aza-5α-androst-1-en-3-one 17β(3-(carbobenzyloxy)propionamidomethyl)- 4-methyl-4-aza-5α-androstan-3-one
25 (16) 	17β(carbomethoxyoctanoylamidomethyl)- 4-methyl-4-aza-5α-androst-1-en-3-one 17β(carbomethoxyoctanoylamidomethyl)- 4-methyl-4-aza-5α-androstan-3-one

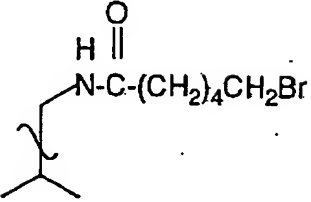
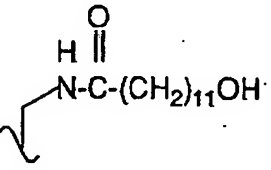
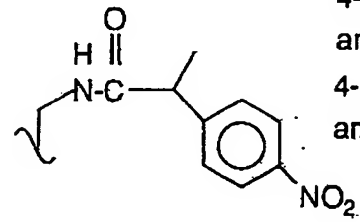
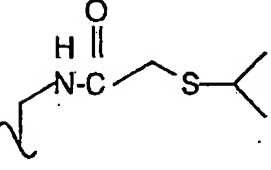
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TABLE 1 (CONT'D)

Side Chain A	Compound(s):
5	
(17) 	17 β (8-(carbomethoxy)octanoylamido)- 4-methyl-4-aza-5 α -androst-1-en-3-one 17 β (8-(carbomethoxy)octanoylamido)- 4-methyl-4-aza-5 α -androstan-3-one
10	
(18) 	17 β (isopropylthiododecanoylamido)- 4-methyl-4-aza-5 α -androst-1-en-3-one 17 β (isopropylthiododecanoylamido)- 4-methyl-4-aza-5 α -androstan-3-one
15	
(19) 	17 β (benzenesulfonamidomethyl)-4-methyl- 4-aza-5 α -androst-1-en-3-one 17 β (benzenesulfonamidomethyl)-4-methyl- 4-aza-5 α -androstan-3-one
20	
25	
30	

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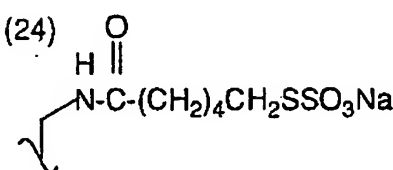
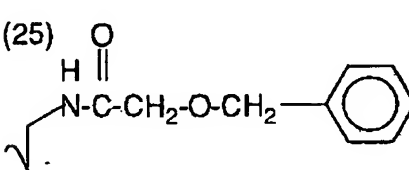
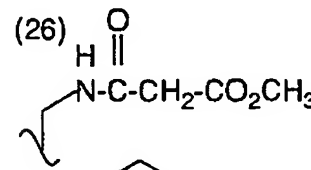
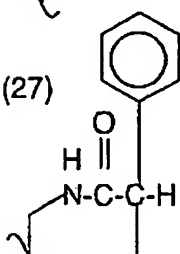
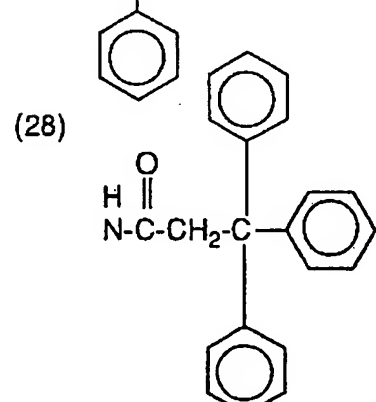
TABLE 1 (CONT'D)

Side Chain A	Compound(s):
<p>5</p> <p>(20)</p> 	<p>17β(6-Bromohexanoylamidomethyl)- 4-methyl-4-aza-5α-androst-1-en-3-one 17β(6-Bromohexanoylamidomethyl)- 4-methyl-4-aza-5α-androstan-3-one</p>
<p>10</p> <p>(21)</p> 	<p>17β(12-hydroxydodecanoylamidomethyl)- 4-methyl-4-aza-5α-androst-1-en-3-one 17β(12-hydroxydodecanoylamidomethyl)- 4-methyl-4-aza-5α-androstan-3-one</p>
<p>15</p> <p>(22)</p> 	<p>4-methyl-17β(2-(4-nitrophenyl)propion- amidomethyl)-4-aza-5α-androst-1-en-3-one 4-methyl-17β(2-(4-nitrophenyl)propion- amidomethyl)-4-aza-5α-androstan-3-one</p>
<p>20</p> <p>(23)</p> 	<p>17β(isopropylthioacetamidomethyl)- 4-methyl-4-aza-5α-androst-1-en-3-one 17β(isopropylthioacetamidomethyl)- 4-methyl-4-aza-5α-androstan-3-one</p>

30

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TABLE 1 (CONT'D)

	Side Chain A	Compound(s):
5	(24) 	4-methyl-17β(thiosulfatohexanoylamido- methyl)-4-aza-5α-androst-1-en-3-one 4-methyl-17β(thiosulfatohexanoylamido- methyl)-4-aza-5α-androstan-3-one
10	(25) 	17β(benzyloxyacetamidomethyl)- 4-methyl-4-aza-5α-androst-1-en-3-one 17β(benzyloxyacetamidomethyl)- 4-methyl-4-aza-5α-androstan-3-one
15	(26) 	17β(carbomethoxyacetamidomethyl)- 4-methyl-4-aza-5α-androst-1-en-3-one 17β(carbomethoxyacetamidomethyl)- 4-methyl-4-aza-5α-androstan-3-one
20	(27) 	17β(diphenylacetamidomethyl)-4-methyl- 4-aza-5α-androst-1-en-3-one 17β(diphenylacetamidomethyl)-4-methyl- 4-aza-5α-androstan-3-one
25	(28) 	4-methyl-17β(3,3,3-triphenylpropionamido- methyl)-4-aza-5α-androst-1-en-3-one 4-methyl-17β(3,3,3-triphenylpropionamido- methyl)-4-aza-5α-androstan-3-one
30		

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The following additional compounds may also be prepared according to the procedures described in the instant specification.

- 5 17B-(2-Furylacetamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
17B-(4-Isopropylphenylacetamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
10 17B-(Cyclohexylacetamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
17B-(3-Indolylacetamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
4-Methyl-17B-(4-Methylcyclohexanecarboxamidomethyl)-4-aza-5 α -androstan-3-one;
15 17B-(4-(3-Indolyl)-butyramidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
17B-(4-Isobutylbenzamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
20 17B-(Acetoxycetamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
17B-(6-Bromohexanoylamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
4-Methyl-20-(4-Nitrobenzamidomethyl)-4-aza-5 α -pregnan-3-one;
25 20-((3-Acetamido)benzamido)-4-Methyl-4-aza-5 α -pregnan-3-one;
20-(3,4-Dimethoxyphenylacetamidomethyl)-4-Methyl-4-aza-5 α -pregnan-3-one;
17B-(4-Ethoxybenzamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
30 4-Methyl-20-(Palmitoylamidomethyl)-4-aza-5 α -pregnan-3-one;
17B-(Iminodibenzyl-5-carboxamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
4-Methyl-20-(Stearoylamido)-4-aza-5 α -pregnan-3-one; 4-Methyl-17B-(3,5-Bis-(Trifluoromethyl)benzamido-methyl)-4-aza-5 α -androstan-3-one;

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- 17 β -(3-Cyanobenzamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
20-(Heptafluorobutyramidomethyl)-4-Methyl-4-aza-5 α -pregnan-3-one;
5 20-(4-Benzoylbenzamidomethyl)-4-Methyl-4-aza-5 α -pregnan-3-one;
17 β -(Benztriazol-5-carboxamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
10 20-(3,5-Difluorobenzamido)-4-Methyl-4-aza-5 α -pregnan-3-one;
17 β -(Bis-(4-Isopropyl)phenyl)acetamidomethyl-4-Methyl-4-aza-5 α -androstan-3-one;
4-Methyl-20-(Salicylamidomethyl)-4-aza-5 α -pregnan-3-one;
17 β -(Cinnamoylamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
15 17 β -((3-Hydroxy-4,4,4-trichlorobutyramido)methyl)-4-Methyl-4-aza-5 α -androstan-3-one.

Synthesis of Testosterone 5- α Reductase Inhibitors:

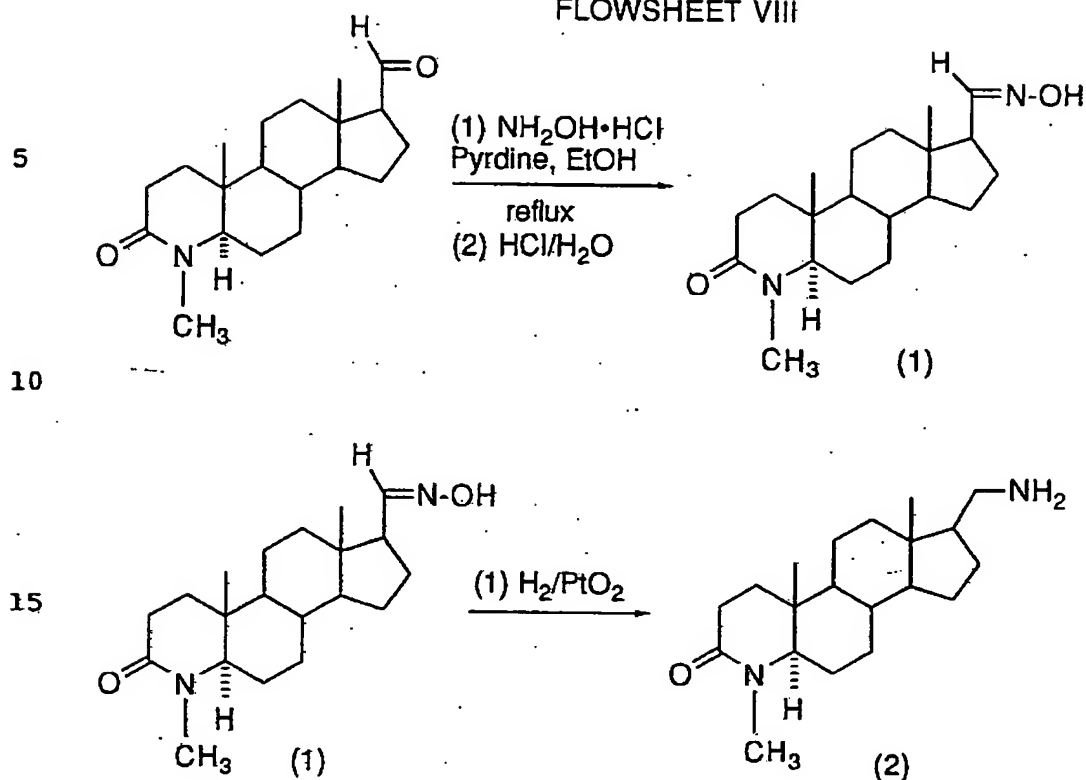
- 20 General flowsheet VIII illustrates the synthesis of the intermediate oximes and amines used to produce compounds claimed in the instant invention.

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FLOWSHEET VIII



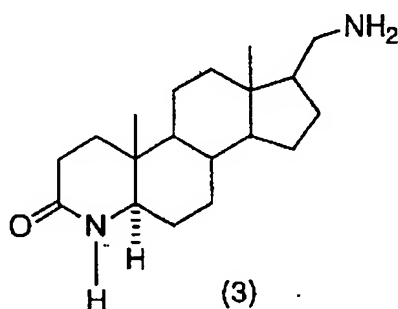
20 A stirred mixture of 4-methyl-3-oxo-5- α -4-azaandrost-17-carboxaldehyde, hydroxylamine hydrochloride, anhydrous pyridine, and anhydrous ethanol is refluxed gently under a nitrogen atmosphere for six to seven hours. After cooling, the ice-cooled mixture is diluted, with stirring, with a slight excess of
 25 chilled dilute hydrochloric acid. The suspension is then aged for about twenty minutes, filtered, washed with water and dried to give compound 1.

30 With reference to flowsheet VIII, a mixture of the oxime (1), ethanol, glacial acetic acid and water is reduced in the presence of platinum oxide (PtO_2) until chromatographic analysis (TLC) indicates complete reduction to the amine (2). The filtered reaction mixture is concentrated in vacuo; the resultant residue is dissolved in chloroform (CHCl_3) and washed with fresh dilute sodium hydrogen carbonate solution. The chloroform phase is then

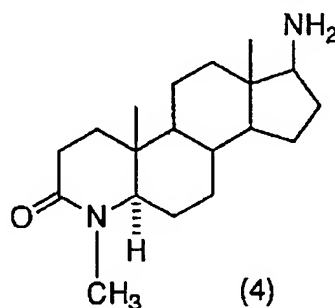
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dried with sodium sulfate (Na_2SO_4). Concentration of the resultant CHCl_3 solution followed by trituration of the residue with hexane/ether will yield 2 as a white solid.

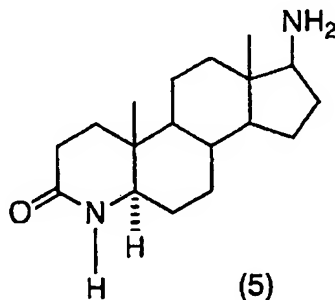
The following amines are representative of those obtained from the corresponding carbonyl compounds utilizing the basic procedures described in flowsheet VIII for preparation of the oximes and amines:



17-Aminomethyl-5-α-4-azaandrostan-3-one;



17-Amino-4-methyl-5-α-4-azaandrostan-3-one;

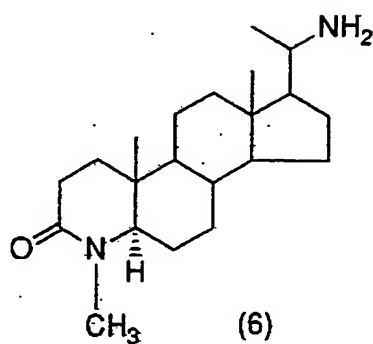


- 128 -

17-Amino-5- α -4-azaandrostan-3-one;

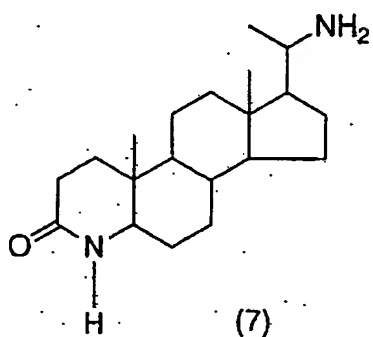
5

10

20-Amino-4-methyl-5- α -4-azapregnan-3-one;

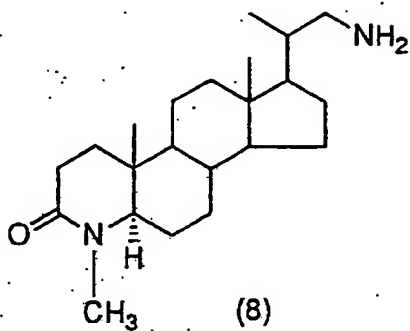
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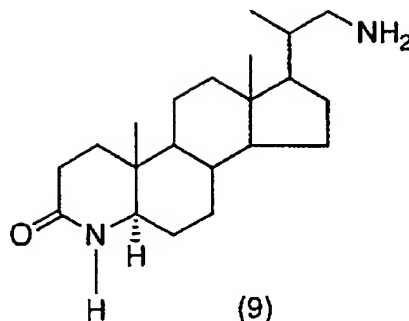
20-Amino-5- α -4-azapregnan-3-one;

25

30

20-(Aminomethyl)-4-methyl-5- α -4-azapregnan-3-one;

- 129 -



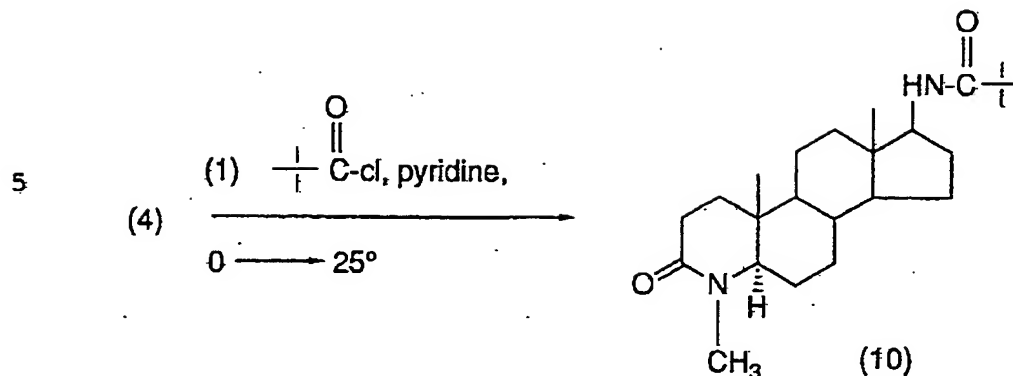
5
10 20-(Aminomethyl)-5- α -4-azapregnan-3-one;

As flowsheet VIII indicates, the oximes useful as intermediates may readily be prepared by reacting 4-azasteroidal aldehyde or ketone with hydroxylamine hydrochloride to form the corresponding oxime. The resultant oximes are subsequently
15 reduced with hydrogen (H_2) and platinum oxide (PtO_2) or other suitable reducing agent to yield the respective amine. The product amides may be further alkylated with, for example, alkyl halides to give the corresponding R^2 alkylated compounds. Alternatively, the primary amines may be alkylated by well known synthetic
20 procedures to the corresponding secondary amines and then acylated to the product amides.

Flowsheet IX illustrates the synthesis of the compound 4-methyl-17(trimethylacetylamido)-5- α -4 azaandrostan-3-one and is representative of a basic synthesis of compounds claimed in the
25 instant invention in which an amine is reacted with an acylating agent (or acid equivalent). These reagents include acyl halides and acid anhydrides.

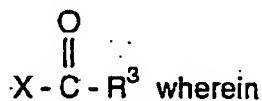
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To a stirred, ice-cold solution of (4), anhydrous methylene chloride and pyridine is added trimethylacetylchloride dropwise over approximately one minute under a nitrogen atmosphere. After an additional fifteen minutes at ice-bath temperatures, the mixture is allowed to warm to room temperature (25°C) and stirred for an additional fourteen hours. The mixture is then transferred to a separatory funnel with additional CH_2Cl_2 , washed with dilute (0.3N) HCl, dried (Na_2SO_4), concentrated and recrystallized (ethyl acetate) to yield 10 as a white solid.

As flowsheet IX illustrates, 4-azasteroidal primary or secondary amines described in the instant invention are reacted with the desired activated carbonyl compound, such as trimethylacetyl chloride, to yield the target amide. Representative acyl halides or acid anhydrides of the formula:



R^3 equals

C_{1-20} alkyl,
aryl,
heteroaryl,

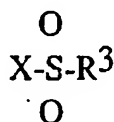
- 131 -

arylC₁₋₂₀alkyl,
 heteroarylC₁₋₂₀alkyl,
 C₁₋₂₀alkylarylC₁₋₂₀alkyl,
 C₁₋₂₀alkyloxycarbonylalkyl,
 C₁₋₂₀alkylcarbonylC₁₋₂₀alkyl,
 C₁₋₂₀cycloalkylC₁₋₂₀alkyl,
 arylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
 haloC₁₋₂₀alkyl,
 arylC₁₋₂₀alkyloxoC₁₋₂₀alkyl,
 diarylC₁₋₂₀alkyl,
 triarylC₁₋₂₀alkyl,
 C₂₋₂₀ alkenyl,
 C₂₋₂₀ alkenylC₁₋₂₀alkyl,
 C₂₋₂₀alkynylC₁₋₂₀alkyl,
 arylC₂₋₂₀alkynylC₁₋₂₀alkyl,
 heteroarylC₂₋₂₀alkynylC₁₋₂₀alkyl,
 or arylC₂₋₂₀alkenyl may be used in the instant invention.

Acyl halides or activated carbonyl compounds disclosed
 in this invention are commercially available or may be prepared
 from the corresponding carboxylic acid and thionyl chloride
 (SOCl₂), phosphorous pentahalide (PX₅), or phosphorous trihalide
 (PX₃). See Ansell in Patai, "The Chemistry of Acyl Halides", 35-48,
 Interscience, New York (1972).

The primary or secondary amines disclosed in the
 instant invention may also be reacted with alkyl and aryl sulfonyl
 halides or anhydrides to yield compounds claimed in the instant
 invention.

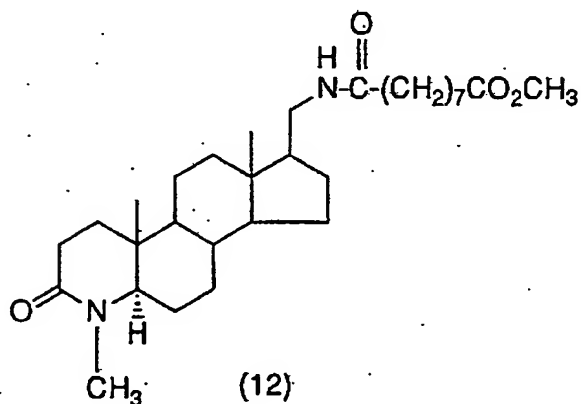
If a sulfonylhalide or anhydride of the formula



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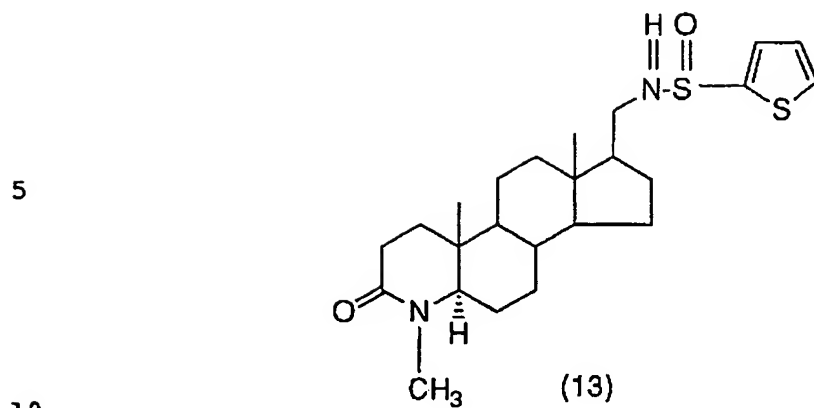
is used, R^3 may equal the groups defined above for the carbonyl species.

Amides or sulfonamides representative of those obtained from the corresponding amines utilizing the basic procedure described in flowsheet IX by substituting either the amine or the activated carbonyl compound may be prepared. For example, compound 6 may be substituted for compound 4 in flowsheet IX and reacted with the indicated acylating agent (trimethylacetyl chloride) to yield compound 11 (4-methyl-20-(trimethylacetamido)-5- α -4-azapregnan-3'-one). If compound 2 is reacted with 8-(carbo-methoxy)octanoyl chloride using the procedure described in flowsheet IX, (17-(8-(Carbomethoxy)-octanoylamidomethyl)-4-methyl-5- α -4-aza-androstan-3-one) is produced:

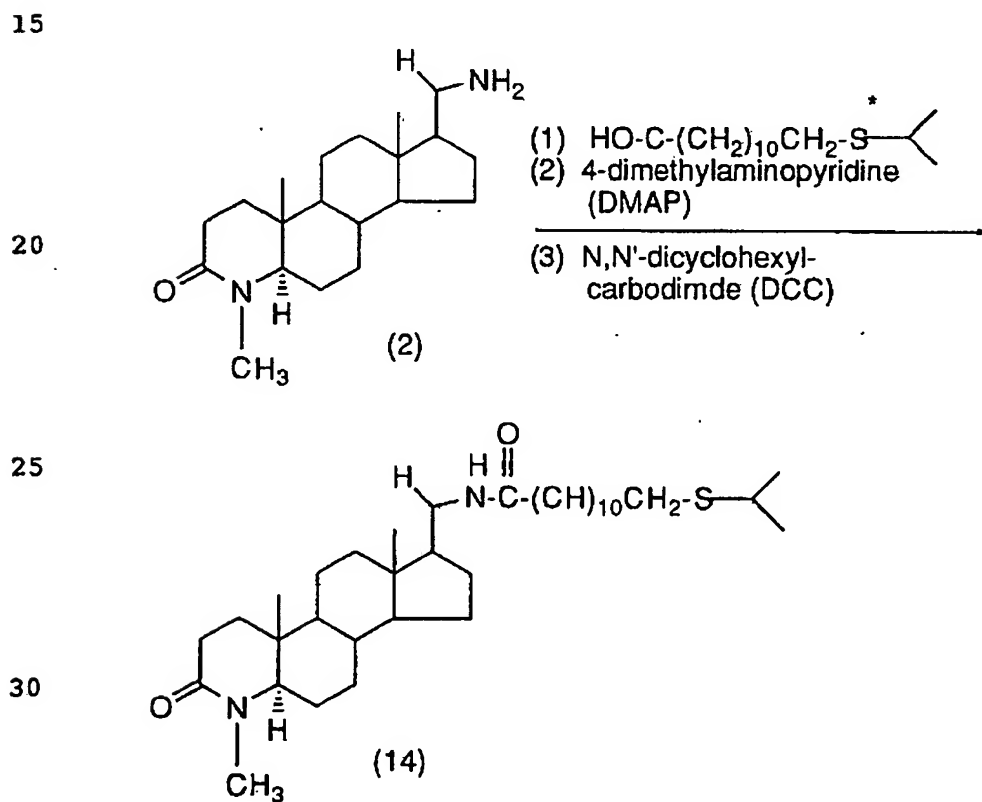


If sulfonyl halide is substituted for an acyl halide and reacted with an amine such as 2, (4-methyl-17-(2-thiophenesulfonylamidomethyl)-5- α -4-azaandrostan-4-one) may be prepared:

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Flowsheet X illustrates the synthesis of 17B-(12-(Isopropyl-thio)dodecanoylamidomethyl)-4-methyl-5 α -aza-androstan-3-one (14):



FLOWSHEET X

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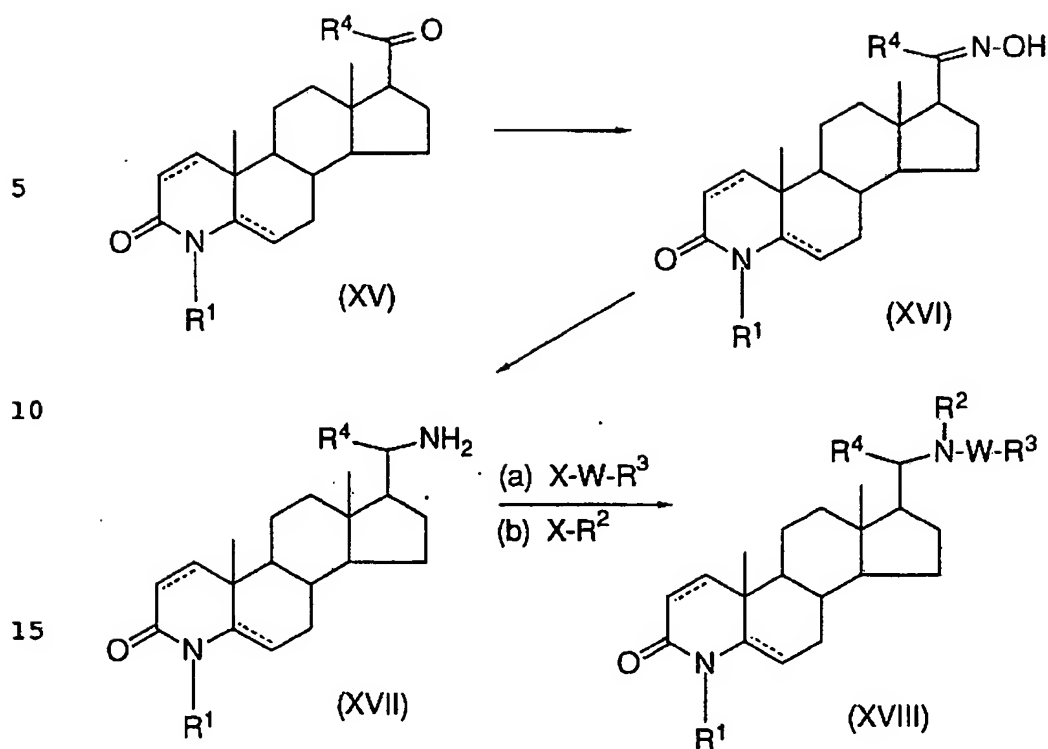
*prepared from 12-bromododecanoic acid and sodium isopropylthiolate

5 DCC is a well known coupling reagent used in peptide synthesis to generate amide bonds from a free acid and an amine. Coupling reagents may generally be used when the free acid is readily available or when the alternative acid halide is internally labile (e.g., when a thio group is present). An intermediate
10 anhydride of the acid is generated which further reacts with the amine. In flowsheet X, 12-(isopropylthio)-dodecanoic acid is reacted with 2, DCC, and DMAP to produce the corresponding amide (14). For example, DCC is used when R^3 is $C_{1-20}alkylthioC_{1-20}alkyl$ or hydroxyl $C_{1-20}alkyl$. Additionally, dehydrogenation of the 1,2
15 position or the 5,6 position may readily be accomplished by known synthetic methodology to produce the claimed 1-en or 5-en derivatives. See U.S. 5,061,802; Dolling et al., JACS, 110, 3318-19 (1988).

20 General flowsheets XI, XII and XIII further illustrate how compounds claimed in the instant invention may be prepared. In flowsheet XI, the starting 4-azasteroid aldehyde or ketone (XV), obtained by known synthetic methods, is reacted to form the oxime (XVI); reduced to the amine (XVII) and reacted with an activated
25 carbonyl or sulfonyl compound and an alkylhalide ($X-R^2$) to form XVIII.

30

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General Flowsheet XI

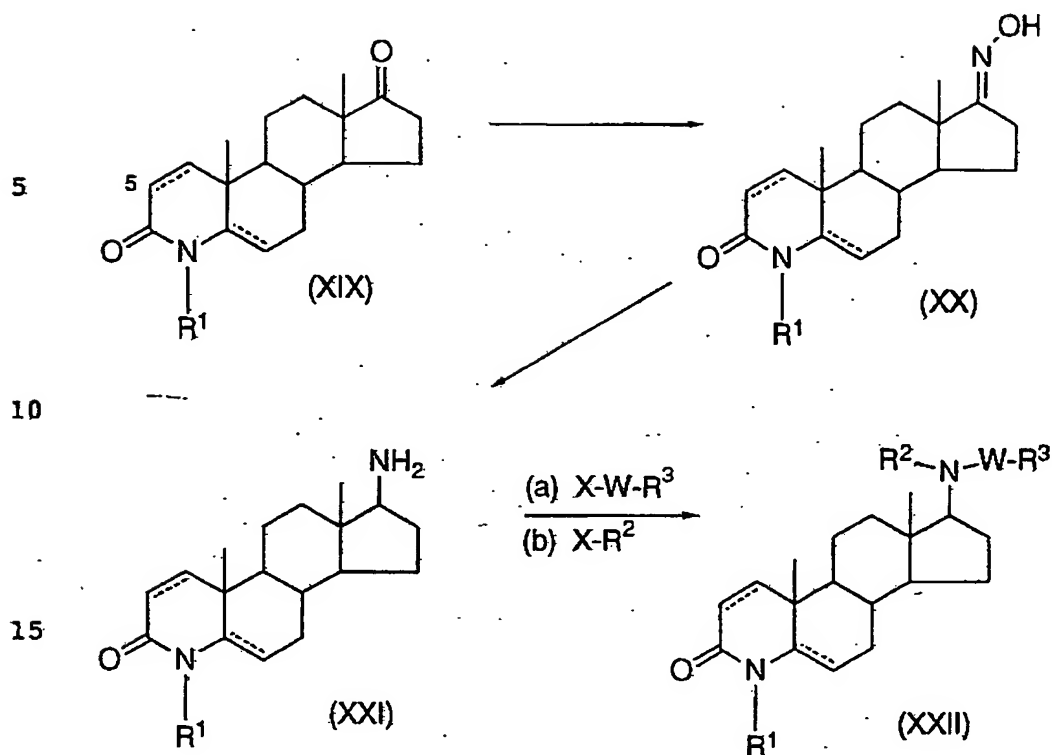
20

In flowsheet XII, the identical procedure is followed using a generic 4-azasteroid (XIX) prepared by known synthetic methods to produce the oxime (XX) which is reduced to the amine (XXI) and reacted with an activated carbonyl or sulfonyl compound (X-W-R³) to yield (XXII).

25

30

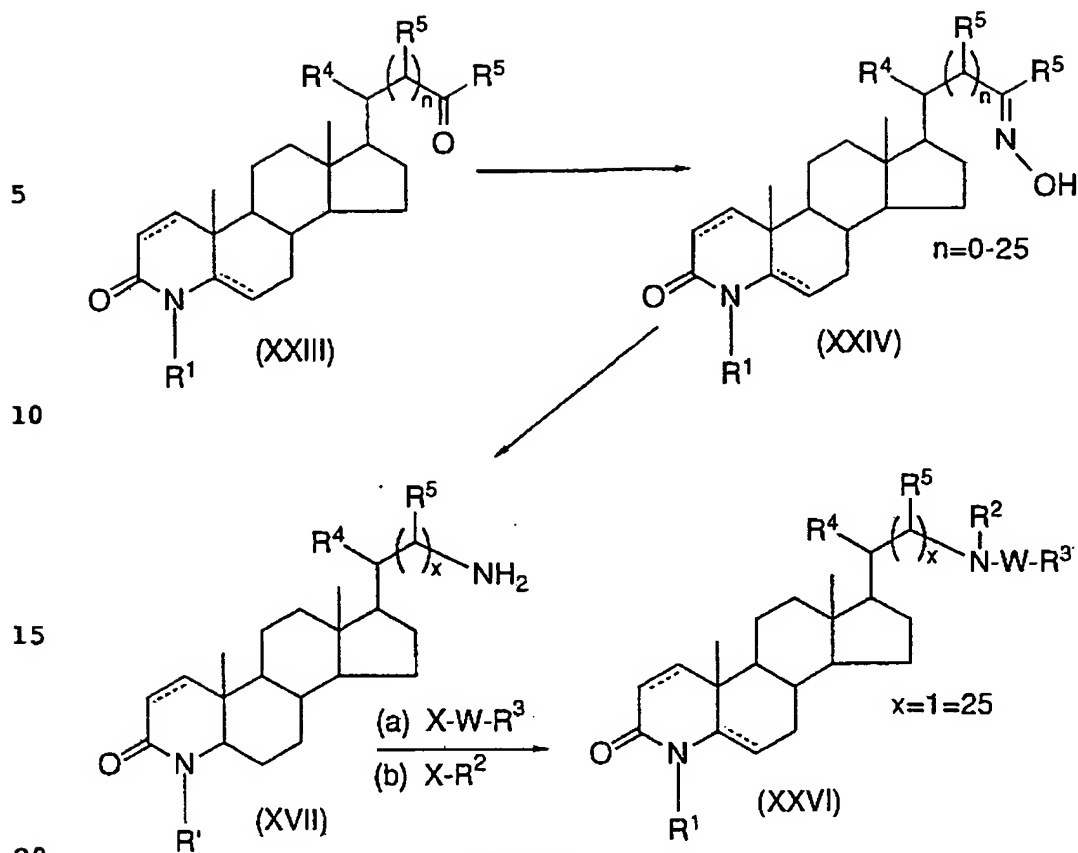
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FLOWSHEET XII

In flowsheet XIII, the generic 4-azasteroid XXIII, also obtained from well known synthetic methodology, is reacted to form the oxime XXIV which is further reduced to form XXV and subsequently reacted with an activated carbonyl or sulfonyl compound to form XXVI.

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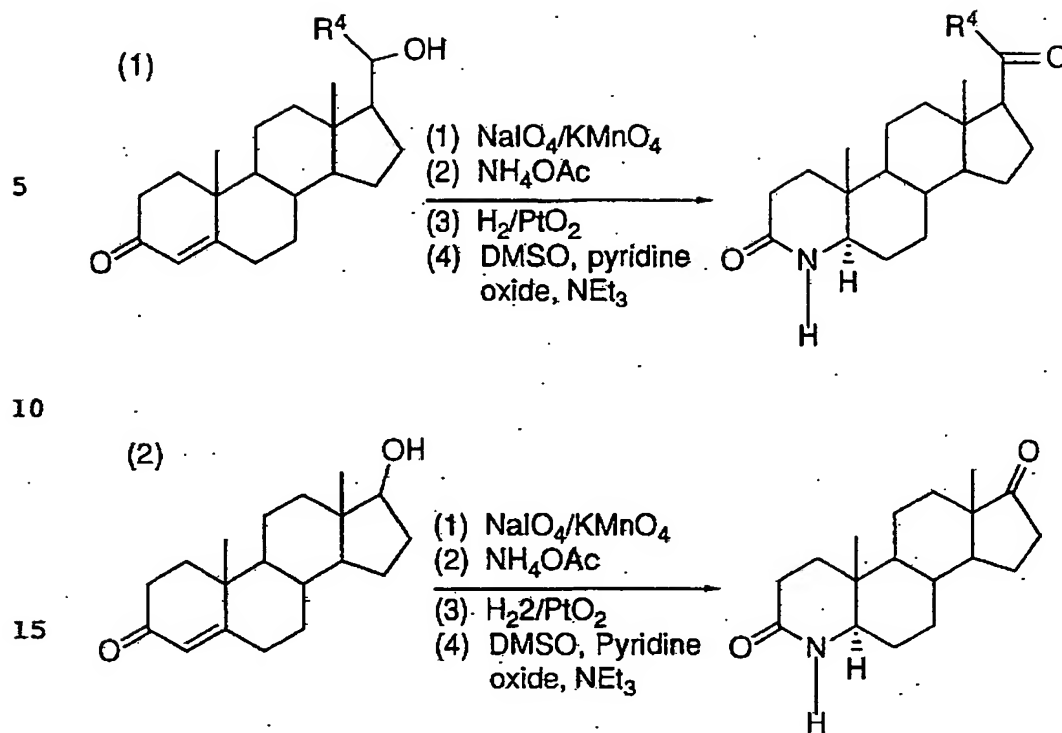
FLOWSHEET XIII

25

30

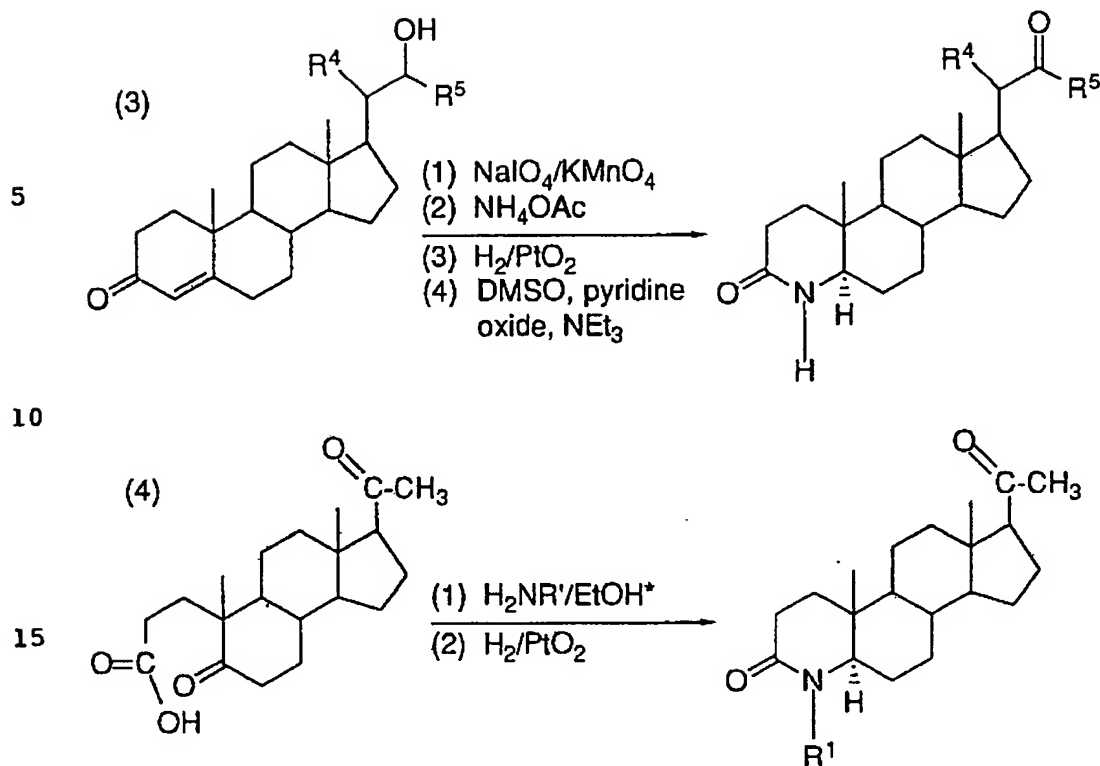
The starting 4-azasteroidal ketones used in the present invention may be prepared according to the well known basic procedures described in flowsheet XIV.

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FLOWSHEET XIV

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* U.S. PAT. NO. 4,377,584

FLWSHEET XIV, CONTINUED

The following examples further describe the synthesis of compounds claimed in the instant invention.

Synthesis of Starting -4-azasteroid oximes:EXAMPLE 9(9) 4-Methyl-3-oxo-5- α -4-azaandrostan-17-carboxaldehyde oxime

A stirred mixture of 4-methyl-3-oxo-5- α -4-azaandrostan-17-carboxaldehyde (0.952 g, 3.0 mM), hydroxylamine hydrochloride (1.10 g, 15.8 mM), anhydrous pyridine (6 mL), and anhydrous ethanol (12 mL) was refluxed gently under a nitrogen

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atmosphere for 6.3 hours. After cooling, the ice-cooled mixture was diluted, with stirring, with a slight excess of chilled dilute hydrochloric acid (ca. 0.3 N), the suspension was aged for ca. 20 minutes, filtered, washed with water and dried to give (9) 0.855 g.
5 MS M^+ calcd for $C_{20}H_{32}H_2O_2$ 332.48. observed m/e 332.

Synthesis of Reactant 4-azasteroid Amines:

10 EXAMPLES 10-17

(10) 17-Aminomethyl-4-methyl-5- α -4-azaandrostane-3-one.

A mixture of (9) (0.67 g., 2.0 mM), ethanol (100 mL), glacial acetic acid (8 mL) and water (4 mL) was reduced in a hydrogen atmosphere (40 p.s.i.) at room temperature in the presence
15 of PtO_2 until TLC analysis indicated complete reduction. The filtered reaction mixture was concentrated in vacuo, the residue taken up in chloroform, and the chloroform solution washed with fresh dilute sodium hydrogen carbonate solution and dried
20 (Na_2SO_4). Concentration of the filtered chloroform solution followed by trituration of the residue obtained with hexane containing a small amount of ether yielded (10) as an off-white solid. MS MH^+ calcd for $C_{20}H_{34}N_2O$ 318.49, observed m/e 319.

25 The following amines are representative of those obtained from the corresponding carbonyl compounds utilizing the above procedures:

(11) 17-Aminomethyl-5- α -4-azaandrostane-3-one.

30 (12) 17-Amino-4-methyl-5- α -4-azaandrostane-3-one.

(13) 17-Amino-5- α -4-azaandrostane-3-one.

(14) 20-Amino-4-methyl-5- α -4-azapregnan-3-one.

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(15) 20-Amino-5- α -4-azapregnan-3-one.

(16) 20-(Aminomethyl)-4-methyl-5- α -4-azapregnan-3-one.

(17) 20-(Aminomethyl)-5- α -4-azapregnan-3-one.

Synthesis of Amino substituted azasteroids:

10

EXAMPLES 18-22

(18) 4-Methyl-17 β -(trimethylacetamido)-5- α -4-azaandrostan-3-one

To a stirred, ice-cold solution of (12) (0.091 g, 0.3 mM), anhydrous methylene chloride (5 mL), and pyridine (0.1 mL, 1.2 mM), was added trimethylacetyl chloride (0.05 mL, 0.4 mM) dropwise over ca. one minute (nitrogen atmosphere). After an additional 15 min. at ice-bath temperatures the mixture was allowed to warm to room temperature and stir at ambient temperature overnight. The mixture was then transferred to a separatory funnel with additional methylene chloride, washed with dilute (ca. 0.3N) hydrochloric acid, and dried (Na₂SO₄). Concentration of the filtered solution followed by recrystallization (ethyl acetate) of the residue obtained gave (18) as a white solid. MS M⁺ calcd for C₂₄H₄₀N₂O₂ 388.59, observed m/e 388.

25

(19) 4-Methyl-20-(trimethylacetamido)-5- α -4-azapregnan-3-one

When (12) in the above reaction was replaced by (14), (19) was obtained as a white solid. MS M⁺ calcd for C₂₆H₄₄H₂O₂ 416.65, observed m/e 416.

30

(20) 17 β -(8-(Carbomethoxy)octanoylamidomethyl)-4-methyl-5- α -4-azaandrostan-3-one.

When (10) was reacted with 8-carbomethoxyoctanoyl chloride using the conditions of Example (18), compound (20) was

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obtained as a thick oil. MS M^+ calcd for $C_{30}H_{50}N_2O_4$ 502.74, observed m/e 502.

5 (21) 4-Methyl-17 β -(2-thiophenesulfonylamidomethyl)-5- α -4-
azaandrostan-3-one.

When the 8-carbomethoxyoctanoyl chloride in the above example was replaced with 2-thiophene- sulfonyl chloride, (21) was obtained as a white solid. MS M^+ calcd for $C_{24}H_{36}N_2O_3S_2$ 464.68,
10 observed m/e 464.

22) 17 β -(12-(Isopropylthio)dodecanoylamidomethyl)-4-methyl-5- α -4-
aza-androstan-3-one

To a stirred solution of (10) (0.028 g, 0.09 mM) and
15 12-(isopropylthio)dodecanoic acid (0.025 g, 0.09 mM) (prepared from 12-bromododecanoic acid and sodium isopropylthiolate by heating in 1,2-dimethoxyethane) in methylene chloride (3 mL) was added 4-(dimethylamino)-pyridine (0.011 g, 0.09 mM) followed by a solution of N,N'-dicyclohexylcarbodiimide (0.020 g, 0.097 mM) in a
20 minimum of the same solvent. After stirring for 12-14 hours, the mixture was filtered and the filtrate concentrated in vacuo. Flash chromatography (silica gel, ethyl acetate as eluant) yielded (22) as a very thick oil. MS MH^+ calcd for $C_{35}H_{62}N_2O_2S$ 574.95, observed m/e 575.

25

Examples 23-45 prepared according to the basic procedures described above further exemplify the invention.

- 30 23) 4-Methyl-17 β -(trimethylacetamidomethyl)-4-aza-5 α -androstan-3-one;
24) 17 β -(acetamido)-4-Methyl-4-aza-5 α -androstan-3-one;
25) 4-Methyl-17 β -(2-thiophenecarboxamidomethyl)-4-aza-5 α -androstan-3-one;
26) 17 β -(2-(4-isobutylphenyl)propionamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;

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- 27) 17 β (8-carboxyoctanoylamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
- 28) 17 β (acetoacetamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
- 5 29) 17 β (1-Adamantylacetamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
- 30) 4-Methyl-17 β (2-thiopheneacetamidomethyl)-4-aza-5 α -androstan-3-one;
- 10 31) 17 β (12-(t-butylthio)dodecanoylamido)-4-Methyl-4-aza-5 α -androstan-3-one;
- 32) 17 β (3-(carbobenzyloxy)propionamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
- 33) 17 β (3,4-dimethoxyphenylacetamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
- 15 34) 17 β (8-(carbomethoxy)octanoylamido)-4-Methyl-4-aza-5 α -androstan-3-one;
- 35) 17 β (isopropylthiododecanoylamido)-4-Methyl-4-aza-5 α -androstan-3-one;
- 20 36) 17 β (benzenesulfonamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
- 37) 17 β (6-Bromohehexanoxylamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
- 38) 17 β (12-hydroxydodecanoylamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
- 25 39) 4-Methyl-17 β (2-(4-nitrophenyl)propionamido-methyl)-4-aza-5 α -androstan-3-one;
- 40) 17 β (isopropylthioacetamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
- 30 41) 4-Methyl-17 β (6-(thiosulfato)hexanoylamidomethyl)-4-aza-5 α -androstan-3-one;
- 42) 17 β (benzyloxyacetamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
- 43) 17 β (carbomethoxyacetamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;

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- 44) 17B(diphenylacetamidomethyl)-4-Methyl-4-aza-5 α -androstan-3-one;
 45) 4-Methyl-17B(3,3,3-triphenylpropionamidomethyl)-4-aza-5 α -androstan-3-one;

5

Table 2 illustrates the NMR data of the above examples.

TABLE 2
NMR DATA (PPM)

10

<u>Example</u>	<u>Angular</u>	<u>Methyls</u>	<u>Miscellaneous</u>
18	0.68,	0.88	1.20 (-NHCOC(CH ₃) ₃)
19	0.72	0.88	1.17 (-NHCOC(CH ₃) ₃)
15 20	0.67,	0.89	3.66 (-CO ₂ CH ₃)
21	0.61,	0.88	2.93 (-4-NCH ₃)
22	0.67,	0.89	1.24 (-SCH(CH ₃) ₂)
		1.28	
23	0.67,	0.88	1.18 (-NHCOC(CH ₃) ₃)
20 24	0.70,	0.88	1.98 (-NHCOCH ₃)
25	0.72,	0.89	2.93 (-4-NCH ₃)
26	0.57,	0.85	2.91 (-4-NCH ₃)
	(split)		
27	0.66,	0.88	2.92 (-4-NCH ₃)
25 28	0.64,	0.88	2.24 (-COCH ₃)
29	0.66,	0.88	2.93 (-4-NCH ₃)
30	0.61,	0.87	3.78 (-COCH ₂ -(C ₄ H ₃ S))
31	0.70,	0.89	1.33 (-SC(CH ₃) ₃)

30

TABLE 2 (CONTD)
NMR DATA (PPM)

Example Angular Methyls Miscellaneous

- 145 -

	32	0.64,	0.88	5.12 (-CO ₂ CH ₂ Ph)
	33	0.60,	0.88	3.52(d) (-Ph-(OCH ₃) ₂)
	34	0.70,	0.89	3.66 (-CO ₂ CH ₃)
5	35	0.70,	0.89	1.24 (-SCH(CH ₃) ₂)
			1.28	
	36	0.57,	0.87	2.91 (-4-NCH ₃)
	37	0.67,	0.88	2.92 (-4-NCH ₃)
	38	0.66,	0.88	2.92 (-4-NCH ₃)
10	39	0.61,	0.86	2.92 (-4-NCH ₃)
		(split)		
	40	0.68,	0.88	1.24 (-SCH(CH ₃) ₂)
			1.28	
	41	0.67,	0.89	2.93 (-4-NCH ₃)
	42	0.65,	0.88	4.56 (-OCH ₂ Ph)
15	43	0.68,	0.89	3.75 (-CO ₂ CH ₃)
	44	0.60,	0.86	4.92 (-COCH(Ph) ₂)

The above examples are non-limiting and suitable acylating agents may readily be substituted according to the methods described in the present invention and reacted with a described amine to form the claimed amides. The following definitions further clarify the present invention.

The term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds of this invention which are generally prepared by the free base with a suitable organic or inorganic acid. Representative salts include the following salts: Acetate, adipate, alginate, aspartate benzenesulfonate, benzoate, bicarbonate, bisulfate borate, butyrate, camsylate, carbonate, camphorate, chloride, citrate, digluconate, fumarate, glucoheptanate, gluconate, glutamate, glycerophosphate, hydrobromide, hydrochloride, hydroiodide, lactate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate.

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The term "pharmaceutically effective amount" shall mean that amount or quantity of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or animal that is being sought by a researcher or clinician or physician.

In the schemes and examples described in this disclosure, various reagent symbols have the following meanings:

PtO₂ is platinum oxide

TLC is thin layer chromatography

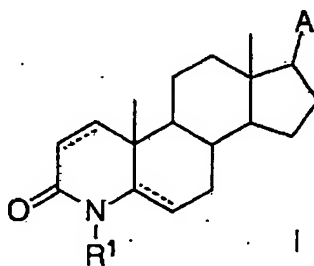
Na₂SO₄ is sodium sulfate

DMAP is 4-(dimethylamino)pyridine

DCC is N,N'-dicyclohexylcarbodiimide

EXAMPLES FOR THE CASE WHEN SUBSTITUENT "A" OF
GENERAL FORMULA "I" IS AS DEFINED IN GROUP "V(A)"

The present invention can utilize compounds of the general structural formula:

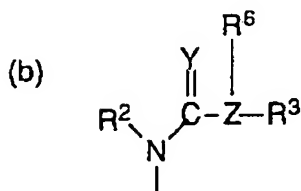
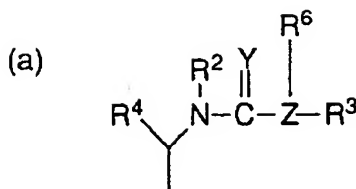


XIV

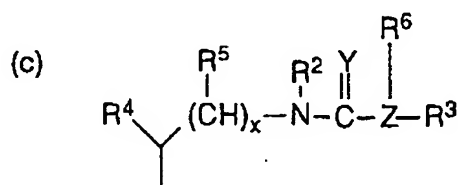
and the pharmaceutically acceptable salts thereof, wherein:

A is:

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except when R^2 equals H, Y equals O, Z equals N, and there is a 5 α H, R^6 and R^3 cannot be independently selected from H, C_{1-8} alkyl, C_{3-6} cycloalkyl, phenyl or when R^6 and R^3 are taken together with the adjacent N to form a 5-6 membered ring comprising up to one other heteroatom selected from O or N, or



; wherein

 R^1 is:

H,
methyl or ethyl;

 R^2 is:

H, or
 C_{1-20} alkyl;

 R^3 is:

H,
 C_{1-20} alkyl,
 C_{6-14} aryl,
heteroaryl,

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5 C₆₋₁₄ arylC₁₋₂₀alkyl,
C₃₋₂₀ cycloalkyl,
C₃₋₂₀ cycloalkylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyl,
C₆₋₁₄ arylcarbonylC₆₋₁₄arylC₁₋₂₀alkyl,
C₂₋₂₀ alkenylC₁₋₂₀alkyl,
haloC₁₋₂₀alkyl,
C₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
10 C₁₋₂₀ alkyloxyC₁₋₂₀alkyl,
carboxyC₁₋₂₀ alkyl,
C₁₋₂₀ alkylcarbonylC₁₋₂₀alkyl,
C₆₋₁₄ arylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
15 hydroxylC₁₋₂₀alkyl,
halohydroxylC₁₋₂₀alkyl,
C₆₋₁₄ arylC₁₋₂₀alkyloxyC₁₋₂₀ alkyl,
heteroarylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
diarylC₁₋₂₀alkyl,
20 triarylC₁₋₂₀alkyl,
C₂₋₂₀ alkenyl,
C₂₋₂₀ alkenylC₁₋₂₀alkyl,
C₂₋₂₀ alkynylC₁₋₂₀alkyl,
C₆₋₁₄ arylC₂₋₂₀alkynylC₁₋₂₀alkyl,
heteroarylC₂₋₂₀alkynylC₁₋₂₀alkyl,
25 C₁₋₂₀ alkylthioC₁₋₂₀alkyl,
C₁₋₂₀ alkylsulfonylC₁₋₂₀alkyl, or
C₁₋₂₀ alkylsulfinylC₁₋₂₀alkyl;

30 R⁴ is:

H,
C₁₋₂₀ alkyl,
heteroaryl, or
C₆₋₁₄ aryl;

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R⁵ can be the same or different when x is greater than 1 and is:

H,
C₁₋₂₀ alkyl,
heteroaryl, or
C₆₋₁₄ aryl;

R⁶ is present when Z equals N and is

H, or
-C₁₋₂₀ alkyl; or taken together with R³ and the N to which they
are attached represent a heteroaryl ring system;

Y is:

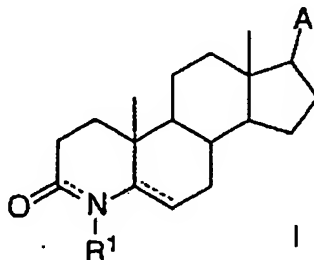
O, or
S;

Z is:

N, or
O;

n is an integer from 1-25,
and dashes indicate a double bond is optionally present.

Advantageously, compounds of the following formula
are disclosed in the present invention.



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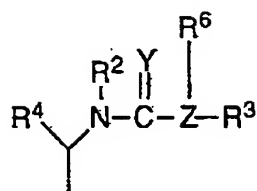
and the pharmaceutically acceptable salts thereof, wherein:

- 150 -

A is:

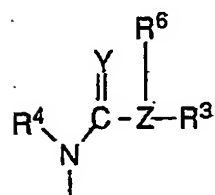
5

(a)



10

(b)

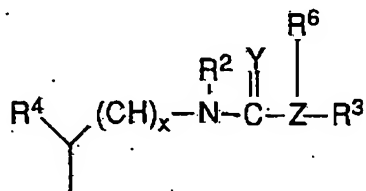


15

except when R^2 equals H, Y equals O, Z equals N and there is a
 5α H, R^6 and R^3 cannot be independently selected from H,
 C_{1-8} alkyl, C_{3-6} cycloalkyl, phenyl or when R^6 and R^3 are
 taken together with the adjacent N to form a 5-6 membered
 ring comprising up to one other heteroatom selected from
 O or N, or

20

(c)



25

; wherein

 R^1 is:

H, or
 methyl or ethyl;

30

 R^2 is:

H, or
 C_{1-20} alkyl;

 R^3 is:

H,

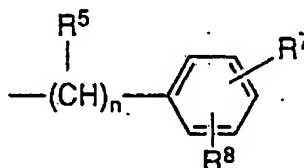
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C₁₋₂₀ alkyl further comprising a straight or branched chain
alkane of up to 20 carbon atoms;

C₆₋₁₄ aryl wherein aryl comprises a mono or polycyclic system
composed of 6-membered aromatic rings either
unsubstituted or substituted with R wherein R comprises H,
C₁₋₂₀ alkyl, arylC₁₋₂₀alkyl with the alkyl groups
unsubstituted or substituted with hydroxyl, C₁₋₈alkyloxy,
carboxy C₁₋₁₀alkyl, or halogen; or aryl can be directly
substituted or multisubstituted independently with
hydroxyl, haloC₁₋₂₀alkyl, benzoyl, C₁₋₂₀alkyloxy, C₁₋₂₀
alkyl, C₂₋₂₀alkenyl, cyano, nitro, carboamide,
acetamide, or halogen;

heteroaryl which comprises a mono or polycyclic system
composed of 5 and 6-membered aromatic rings containing
1, 2, 3 or 4 heteroatoms chosen from N, O, or S and either
unsubstituted or substituted with R as defined for aryl or
substituted or multisubstituted independently with
hydroxyl, C₁₋₂₀ alkyloxy, C₁₋₂₀alkyl, benzyl, carboamide,
acetamide, C₂₋₂₀alkenyl, cyano, nitro, haloC₁₋₂₀alkyl, or
halogens, directly bonded to the aromatic carbon atom(s);

C₆₋₁₄ arylC₁₋₂₀alkyl of the formula:



wherein the aromatic ring is optionally and
independently substituted with R⁷ and R⁸ wherein R⁷ and R⁸
comprise

H,
CH₃,
C₂H₅,

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carboamide,

OH,

OCH₃,NO₂,

5

CN,

F,

RS, RSO, RSO₂, R₂N, where R can be the same or different and
is selected from: H, C1-C4alkyl, C6-C14 aryl;

Cl,

10

acetamido,

OC₂H₅,CF₃,

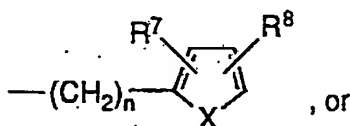
isopropyl, or

isobutyl; n equals 1-10 and the C₁₋₂₀alkyl portion is optionally
substituted with R⁷;

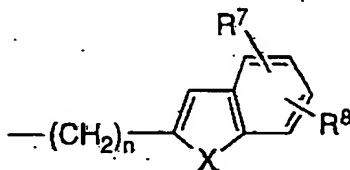
15

HeteroarylC₁₋₂₀alkyl further comprising the formula:

20



25



wherein X equals O, S, or NR; and n equals 1-20;

C₁₋₂₀alkylsulfonylC₁₋₂₀alkyl,

30 C₁₋₂₀alkylthioC₁₋₂₀alkyl,

C₁₋₂₀alkylsulfinylC₁₋₂₀alkyl, comprising the formula:

-(CH₂)_nS(O)_p-R⁹ wherein R⁹ comprises

CH₃,

- 153 -

C₂H₅,
 C₃H₇,
 C₄H₉,
 isopropyl,
 5 isobutyl,
 sec-butyl,
 t-butyl,
 isopentyl,
 10 neopentyl, or
 isohexyl; n equals 1-20; p = 0 1, or 2;

C₁₋₂₀ alkyloxycarbonylC₁₋₂₀alkyl further comprising the formula:

15
$$-(\text{CH}_2)_n-\overset{\text{O}}{\underset{|}{\text{C}}}-\text{OR}^{10}$$
 wherein R¹⁰
 comprises:
 CH₃,
 C₂H₅,
 20 C₃H₇,
 C₄H₉, or
 C₅H₁₁; n equals 1-20;

carboxylC₁₋₂₀ alkyl further comprising:

25
$$-(\text{CH}_2)_n-\overset{\text{O}}{\underset{|}{\text{C}}}-\text{OH}; n \text{ equals } 1-20;$$

C₁₋₂₀alkylcarbonylC₁₋₂₀ alkyl further comprising

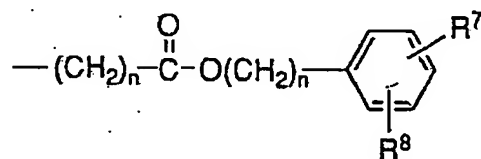
30
$$-(\text{CH}_2)_n-\overset{\text{O}}{\underset{|}{\text{C}}}-\text{(CH}_2\text{)}_m-\text{CH}_3, n \text{ equals } 1-20; m \text{ equals } 0-19;$$

C₁₋₂₀ cycloalkylC₁₋₂₀ alkyl of the formula:

- 154 -

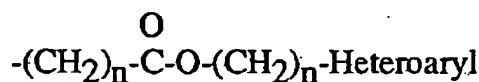
-(CH₂)_n-(cycloalkyl) wherein the cycloalkyl portion comprises monocyclic, bicyclic, or polycyclic hydrocarbons of up to 20 carbon atoms wherein the rings are optionally substituted with R¹, and n equals 1-20;

C₆₋₁₄ arylC₁₋₂₀ alkyloxycarbonylC₁₋₂₀ alkyl of the formula:



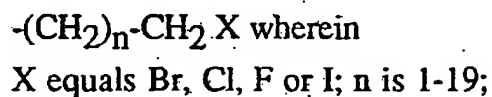
wherein R⁷ and R⁸ are as defined; n equals 1-20;

HeteroarylC₁₋₂₀ alkyloxycarbonylC₁₋₂₀ alkyl of the formula:

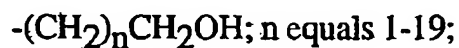


wherein Heteroaryl is as defined; n equals 1-20;

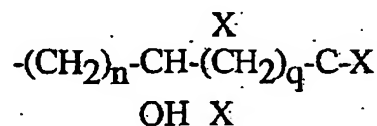
haloC₁₋₂₀ alkyl of the formula:



hydroxylC₁₋₂₀ alkyl of the formula:



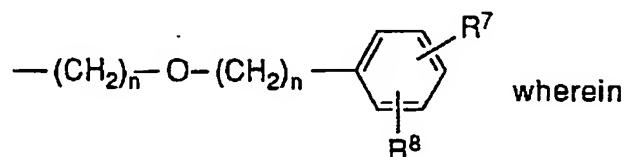
halohydroxylC₁₋₂₀ alkyl of the formula:



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wherein X equals Br, Cl, F or I; $n = 0-18$, $q = 0-18$;
 $n + q = 0-18$;

5 C_{6-14} aryl C_{1-20} alkyloxy C_{1-20} alkyl of the formula:

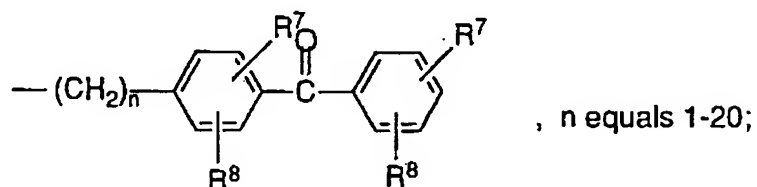


10

R^7 and R^8 are as defined; n is 1-20;

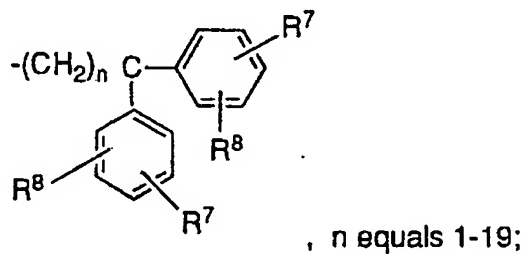
Arylcarbonylaryl C_{1-20} alkyl of the formula:

15



20 Diaryl C_{1-20} alkyl of the formula:

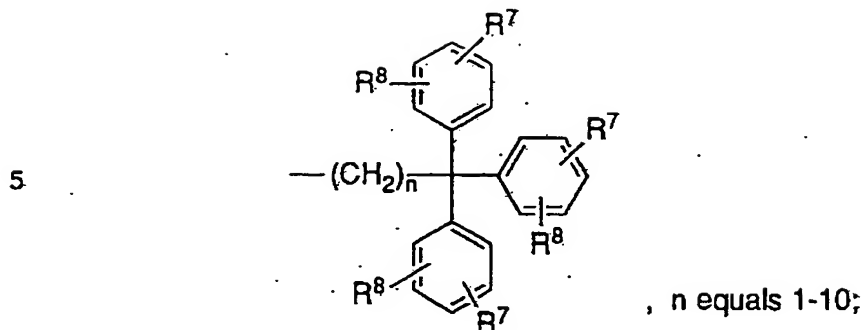
25



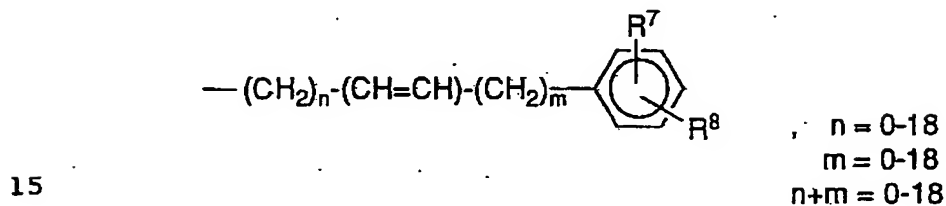
Triaryl C_{1-20} alkyl of the formula:

30

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10 ArylC₂₋₂₀ alkenyl of the formula:



R⁴ is:

20 H,
C₁₋₂₀alkyl,
C₆₋₁₄ aryl, or
Heteroaryl;

R⁵ is:

25 H, or
C₁₋₁₂ alkyl;

R⁶ is present when Z equals N and is independently

30 H,
C₁₋₂₀ alkyl,
equivalent to R³; or taken together with R³ and the N to which
they are attached represent a heteroaryl ring system;

Y is:

O, or
S;

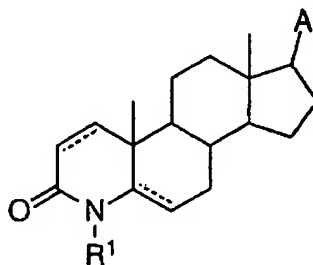
- 157 -

Z is

N, or
O;

x is an integer from 1-10,
dashes indicate a double bond is optionally present.

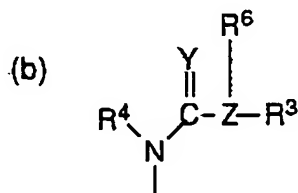
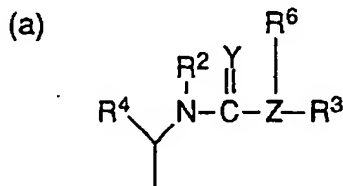
The present invention is further concerned with
compounds of the formula:



XVI

and the pharmaceutically acceptable salts thereof, wherein

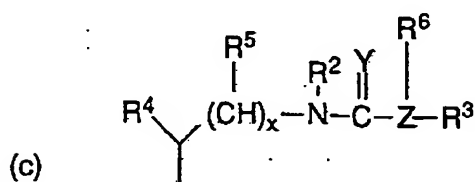
A is:



except when R^2 equals H, Y equals O, Z equals N, and there is a
 5α H, R^6 and R^3 may not be independently selected from

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H, C₁₋₈ alkyl, C₃₋₆ cycloalkyl, phenyl or when R⁶ and R³ are taken together with the adjacent N to form a 5-6 membered ring comprising up to one other heteroatom selected from O or N, or



; wherein

R¹ is:

H,
methyl or ethyl;

R² is:

H, or
C₁₋₂₀ alkyl;

R³ is:

H,
C₁₋₂₀ alkyl,
C₆₋₁₂ aryl,
heteroaryl,
C₆₋₁₂ arylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyl,
C₃₋₂₀ cycloalkyl,
C₃₋₂₀ cycloalkylC₁₋₂₀alkyl,
C₂₋₂₀ alkenylC₁₋₂₀alkyl,
haloC₁₋₂₀alkyl,
C₁₋₂₀ alkyloxyC₁₋₂₀alkyl,
C₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
C₁₋₂₀ alkylthioC₁₋₂₀alkyl,
C₁₋₂₀ alkylsulfonylC₁₋₂₀alkyl,
C₁₋₂₀alkylsulfinylC₁₋₂₀alkyl,
carboxyC₁₋₂₀ alkyl,

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5 C₆₋₁₂ arylcarbonylarylC₁₋₂₀alkyl
C₁₋₂₀ alkylcarbonylC₁₋₂₀alkyl,
C₆₋₁₂ arylC₁₋₂₀ alkyloxy carbonylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyloxy carbonylC₁₋₂₀alkyl,
haloC₁₋₂₀alkyl,
hydroxyC₁₋₂₀alkyl,
halohydroxylC₁₋₂₀alkyl,
10 C₆₋₁₄ arylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
diarylC₁₋₂₀alkyl,
triarylC₁₋₂₀alkyl,
C₂₋₂₀ alkenyl,
C₂₋₂₀ alkenylC₁₋₂₀alkyl,
15 C₂₋₂₀ alkynylC₁₋₂₀alkyl,
C₆₋₁₄ arylC₂₋₂₀alkynylC₁₋₂₀alkyl, or
heteroarylC₂₋₂₀alkynylC₁₋₂₀alkyl;

R⁴ is:

20 H,
C₁₋₂₀ alkyl,
heteroaryl, or
C₆₋₁₄ aryl;

R⁵ is:

25 H,
C₁₋₂₀ alkyl,
heteroaryl, or
C₆₋₁₄ aryl;

30 R⁶ is present when Z equals N and is

H, or
C₁₋₂₀ alkyl; or taken together with R³ and the N to which they
are attached represent a heteroaryl ring system;

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Y is:

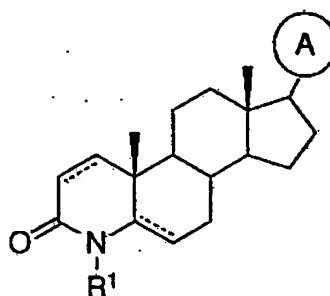
O, or
S;

Z is:

N, or
O;

x is an integer from 1-25, and dashes indicate a double bond is optionally present.

Compounds of the formula



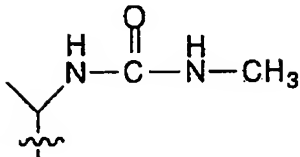
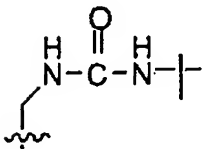
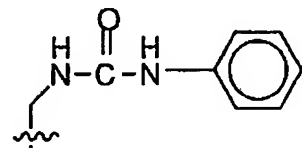
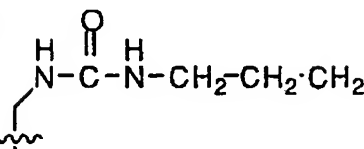
XVIA

are likewise representative of preferred embodiment compounds claimed in the instant invention. In a preferred embodiment, R¹ may be H or CH₃ and A may be as indicated as in Table 3.

Particular representative chemical names are also listed in Table 3 adjacent to the respective side chain and specifically reflect whether the 1-position is saturated or unsaturated. Advantageously, R¹ is CH₃, A is as indicated in Table 3 and the 1 position is saturated.

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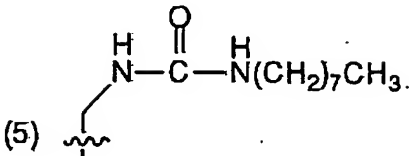
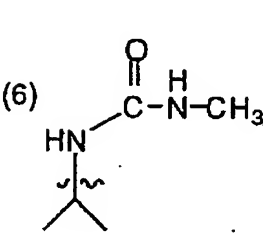
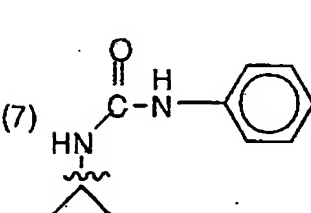
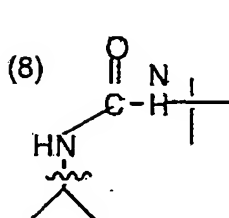


TABLE 3

<u>Side Chain A</u>	<u>Compound(s):</u>
5 (1) 	4-methyl-20-(N'-methyl-ureido)-5 α -4-azapregn-1-en-3-one 4-Methyl-20-(N'-methyl-uriedo)-5 α -4-azapregnane-3-one
10 (2) 	17-(N'-t-butylureido-methyl)-4-methyl-5 α -4-azaandrost-1-en-3-one 17-(N'-t-butylureido-methyl)-4-methyl-5 α -4-azaandrostan-one
15 (3) 	4-Methyl-17-(N'-phenyl-ureidomethyl)-5 α -4-aza-androst-1-en-3-one 4-Methyl-17-(N'-phenyl-ureidomethyl)-5 α -4-aza-androstan-3-one
20 (4) 	4-Methyl-17-(N'-n-propyl-ureidomethyl)-5 α -4-aza-androst-1-en-3-one 4-Methyl-17-(N'-n-propyl-ureidomethyl)-5 α -4-aza-androstan-3-one

30

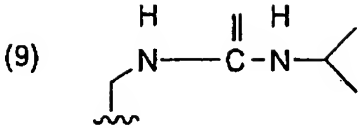
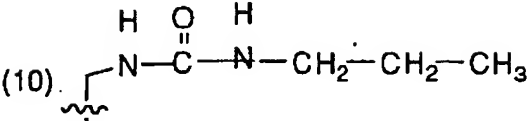
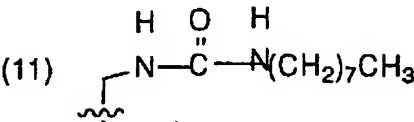
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TABLE 3 (CONT'D)

Side Chain A	Compound(s):
<p>5</p> <p>(5) </p>	<p>4-Methyl-17-(N'-n-octyl-ureidomethyl)- 5α-4-aza-androst-1-en-3-one 4-Methyl-17-(N'-n-octyl-ureidomethyl)- 5α-4-aza-androst-an-3-one</p>
<p>10</p> <p>(6) </p>	<p>4-Methyl-17-(N'-methyl-ureido)-5α- 4-azaandrost-1-en-3-one 4-Methyl-17-(N'-methyl-ureido)-5α- 4-azaandrostan-an-3-one</p>
<p>15</p> <p>(7) </p>	<p>4-Methyl-17-(N'-phenyl-ureido)-5α- 4-azaandrost-1-en-3-one 4-Methyl-17-(N'-phenyl-ureido)-5α- 4-aza-androstan-3-one</p>
<p>20</p> <p>(8) </p>	<p>17-(N'-t-butylureido)4-methyl-5α- 4-azaandrost-1-en-3-one 17-(N'-t-butylureido)4-methyl-5α- 4-azaandrostan-1-en-3-one</p>
<p>25</p> <p>(8) </p>	
<p>30</p> <p>(8) </p>	

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TABLE 3 (CONT'D)

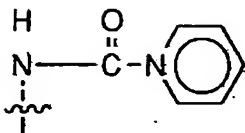
5	(9)		17-(N'-t-isopropylureido- methyl)4-methyl-5 α -4- aza-androst-1-en-3-one
10			17-(N'-t-isopropylureido- methyl)4-methyl-5 α -4- aza-androstan-3-one
15	(10)		4-Methyl-17 β -(N'-n-propyl- ureidomethyl) 5 α -4-aza- androstan-3-one
20	(11)		4-Methyl-17 β -(N'-n-octyl- ureidomethyl)5 α -4-azaan- drostan-3-one

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TABLE 3 (CONT'D)

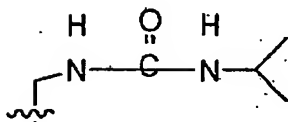
5

(12)

4-Methyl-17 β -(N'-phenyl-ureido)-5 α -4-azaandrost-
an-3-one4-Methyl-17 β -(N'-phenyl-ureido)-5 α -4-azaandrost-
1-en-3-one

10

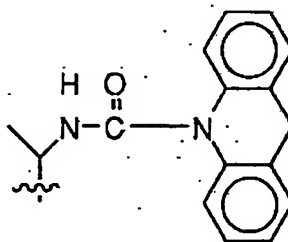
(13)

17 β -(N'-Isopropylureido-methyl)-4-methyl-5 α -4-
azaandrost-3-one17 β -(N'-Isopropylureido-methyl)-4-methyl-5 α -4-
azaandrost-3-one

15

20

(14)

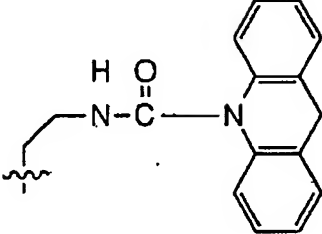
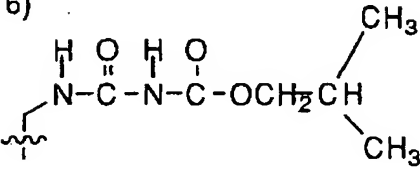
20-((Iminodibenz-5-yl)-
carbonylaminomethyl)-4-
methyl-5 α -4-aza-pregan-
3-one20-((Iminodibenz-5-yl)-
carbonylaminomethyl)-4-
methyl-5 α -4-aza-pregn-1-
en-3-one

25

30

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TABLE 3 (CONT'D)

Side Chain (A)	Compound(s)
<p>(15)</p> 	<p>17β-((Iminodibenz-5-yl)-carbonylaminomethyl)-4-methyl-5α-4-aza-androstan-3-one</p> <p>17β-((Iminodibenz-5-yl)-carbonylaminomethyl)-4-methyl-5α-4-aza-androstan-3-one</p>
<p>(16)</p> 	<p>17β-(Isobutyloxycarbonylaminomethyl)-4-methyl-5α-4-azaandrostan-3-one</p> <p>17β-(Isobutyloxycarbonylaminomethyl)-4-methyl-5α-4-azaandrost-1-en-3-one</p>

The following additional compounds may also be prepared according to the procedures described in the instant specification.

- 20-(Ethoxycarbonylamino)-4-methyl-5- α -4-azapregnan-3-one,
 20-(Benzyloxycarbonylaminomethyl)-5- α -4-azapregnan-3-one,
 4-Methyl-17 β -(N'-octadecylureidomethyl)-5- α -4-aza-androstan-3-one,
 17 β -(N'-Benzylureidomethyl)-5- α -4-azaandrostan-3-one,
 4-Methyl-17 β -(N'-methylureido)-5- α -4-azaandrostan-3-one,
 4-Methyl-17 β -(Isobutyloxycarbonylamino)-5- α -4-aza-androstan-3-one,
 17 β -(N'-(2-Ethylphenyl)ureidomethyl)-5- α -4-aza-androstan-3-one,

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17B-(N'-Allylureido)-4-methyl-5- α -4-azaandrostan-3-one,
20-(N'-(3-Chlorophenyl)ureido)-5- α -4-azapregnan-3-one,
4-Methyl-20-(N'-phenylureido)-5- α -4-azapregnan-3-one,
5 20-(N'-p-Tolylureidomethyl)-5- α -4-azapregnan-3-one,
17B-(N'-(2,3,-Dichlorophenyl)ureidomethyl)-4-methyl-5- α -4-
azaandrostan-3-one,
17B-(N'-(4-Fluorophenyl)ureido)-5- α -4-azaandrostan-3-one,
20-(N'-(2-Ethoxyphenyl)ureidomethyl)-4-methyl-5- α -4-aza-
pregnan-3-one,
10 17B-(N'-(3-Methoxyphenylureido)-5- α -4-azaandrostan-3-one,
4-Methyl-17B-(N'-(naphth-2-yl)ureidomethyl)-5- α -4-
azaandrostan-3-one,
4-Methyl-17B-(N'-thiazol-2-ylureidomethyl)-5- α -4-aza-
androstan-3-one,
15 4-Methyl-20-(N'-thien-2-ylmethylureido)-5- α -4-aza-pregnan-3-
one.

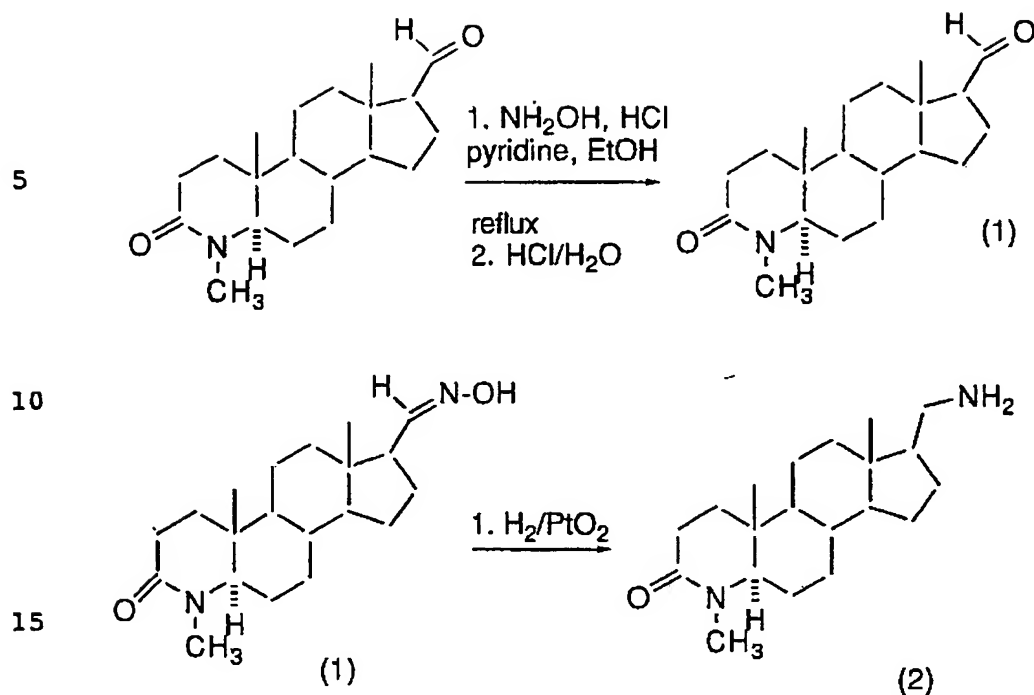
Synthesis of Testosterone 5 α Reductase Inhibitors

20 Flowsheet XV illustrates the synthesis of intermediate
oximes and amines used to produce compounds claimed in the instant
invention.

25

30

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Flowsheet XV

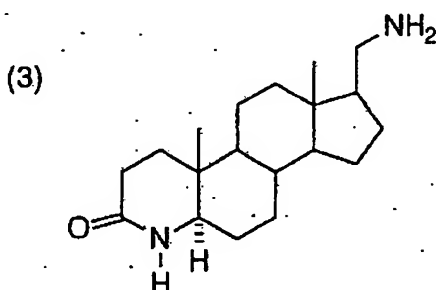
20 A stirred mixture of 4-methyl-3-oxo-5α-4-azaandrostan-17 carboxaldehyde, hydroxylamine hydrochloride, anhydrous pyridine, and anhydrous ethanol is refluxed gently under a nitrogen atmosphere for six to seven hours. After cooling, the ice-cooled mixture is diluted, with stirring, with a slight excess of
 25 chilled dilute hydrochloric acid. The suspension is then aged for about twenty minutes, filtered, washed with water and dried to give compound 1.

A mixture of the oxime (1), ethanol, glacial acetic acid and water is reduced in the presence of platinum oxide (PtO₂) until
 30 chromatographic analysis (TLC) indicates complete reduction to the amine (2). The filtered reaction mixture is concentrated in vacuo; the resultant residue is dissolved in chloroform (CHCl₃) and washed with fresh dilute sodium hydrogen carbonate solution. The chloroform phase is then dried with sodium sulfate (Na₂SO₄).

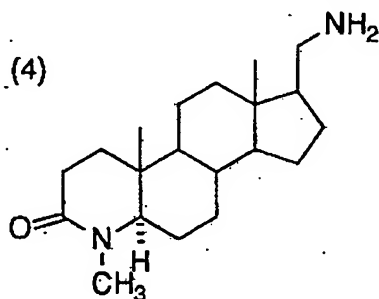
- 168 -

Concentration of the resultant CHCl_3 solution followed by trituration of the residue with hexane/ether will yield 2 as a white solid.

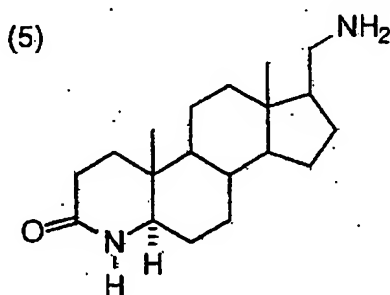
The following amines (3-9) may readily be prepared according to the above process to yield the indicated compounds:



17-Aminomethyl-5-α-2,4-azaandrostan-3-one:

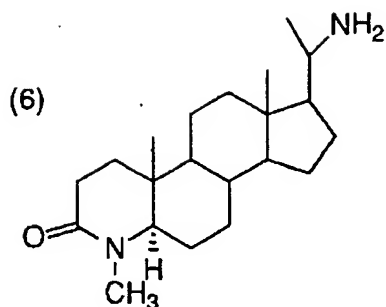


17-Amino-4-methyl-5-α-2,4-azaandrostan-3-one:

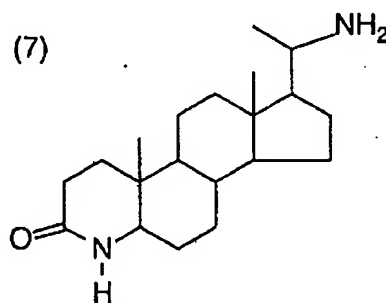


17-Amino-5-α-2,4-azaandrostan-3-one:

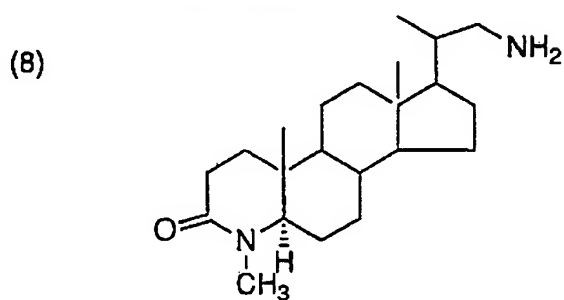
- 169 -



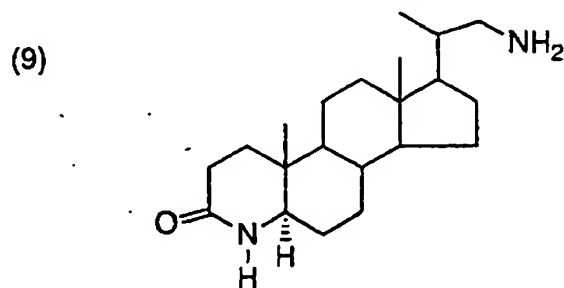
20-Amino-4-methyl-5- α -4-azapregnan-3-one:



20-Amino-5- α -4-azapregnan-3-one:



20-(Aminomethyl)-4-methyl-5- α -4-azapregnan-3-one:

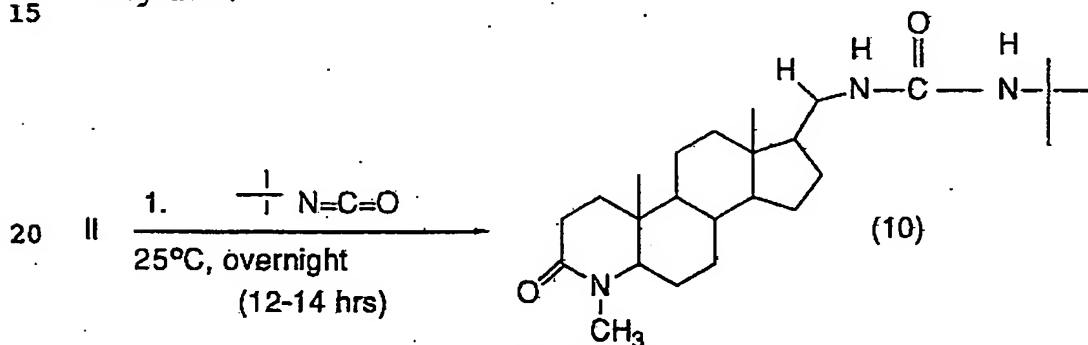


- 170 -

20-(Aminomethyl)-5- α -4-azapregnan-3-one:

As flowsheet XV indicates, the oximes useful as intermediates may readily be prepared by reacting a 4-azasteroidal aldehyde or ketone with hydroxylamine hydrochloride to form the corresponding oxime. The resultant oximes are subsequently reduced with hydrogen (H_2) and platinum oxide (PtO_2) or other suitable reducing agent to yield the respective amine. Product ureas or thioureas may be further alkylated with, for example, alkyl halides to give the corresponding R^2 alkylated compounds.

Flowsheet XVI illustrates the synthesis of the compound 17-(N'-t-butylureidomethyl)-4-methyl-5 α -4-azaandrostan-3-one and is representative of a basic synthesis of compounds claimed in the instant invention in which an amine is reacted with a substituted isocyanate.



FLOWSHEET XVI

To a stirred solution of 2 in dry benzene at room temperature (25°C) is added t-butylisocyanate. After stirring for 12-14 hours, the benzene is removed and purified by flash chromatography (silica gel, EtOAc) to give 10 as a white solid. As flowsheet XVI illustrates, 4-azasteroidal primary or secondary amines described in the instant invention are reacted with the desired substituted isocyanate, such as t-butyl isocyanate, to yield the target ureido derivative.

Representative substituted isocyanates of the formula:



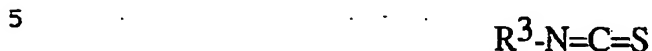
- 171 -

wherein R³ equals

- 5 H,
C₁₋₂₀ alkyl,
aryl,
heteroaryl,
arylC₁₋₂₀alkyl,
C₃₋₂₀ cycloalkyl,
10 C₃₋₂₀ cycloalkylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyl,
C₂₋₂₀ alkenylC₁₋₂₀alkyl,
haloC₁₋₂₀alkyl,
halohydroxylC₁₋₂₀alkyl,
15 C₁₋₂₀ alkyloxyC₁₋₂₀alkyl,
C₁₋₂₀ alkylcarbonylC₁₋₂₀alkyl,
C₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
arylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
20 hydroxyC₁₋₂₀alkyl,
arylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
arylcarbonylarylC₁₋₂₀alkyl,
diarylC₁₋₂₀alkyl,
25 triarylC₁₋₂₀alkyl,
C₂₋₂₀ alkenyl,
C₂₋₂₀ alkenylC₁₋₂₀alkyl,
C₂₋₂₀ alkynylC₁₋₂₀alkyl,
arylC₂₋₂₀alkynylC₁₋₂₀alkyl,
heteroarylC₂₋₂₀alkynylC₁₋₂₀alkyl,
30 C₁₋₂₀ alkylthioC₁₋₂₀alkyl,
C₁₋₂₀ alkylsulfonylC₁₋₂₀alkyl, or
C₁₋₂₀ alkylsulfinylC₁₋₂₀alkyl;

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The primary or secondary amines disclosed in the instant invention may also be reacted with thioisocyanates of the formula



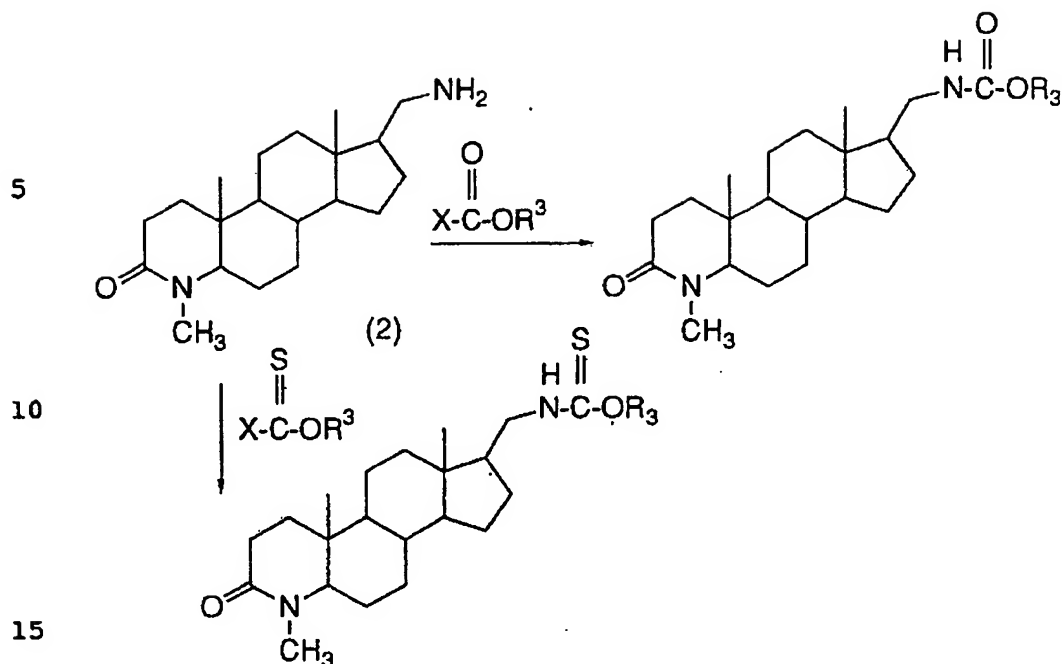
to yield compounds claimed in the instant invention. In addition, as flowsheet XVII shows, the described primary or secondary amines disclosed in the invention (such as 2) may be reacted with activated esters or thioesters to yield compounds claimed in the instant
10 invention. R^3 is defined as above.

Substituted isocyanates or thioisocyanates may readily be prepared by known synthetic methods. For example, phosgene or thiophosgene may be reacted with a suitable primary amine to give a
15 chloroformamide or chloro sulfamide which loses HCl to form the respective substituted isocyanate or thioisocyanate. For reviews of isocyanate and thioisocyanate preparation, see Patai, "The Chemistry of Cyanates and their thio Derivatives," pt 2, Wiley, New York, pp 619-818 and 1003-1221 (1977). In addition, the isocyanates,
20 thioisocyanates, esters or thioesters used to prepare the claimed compounds are commercially available.

25

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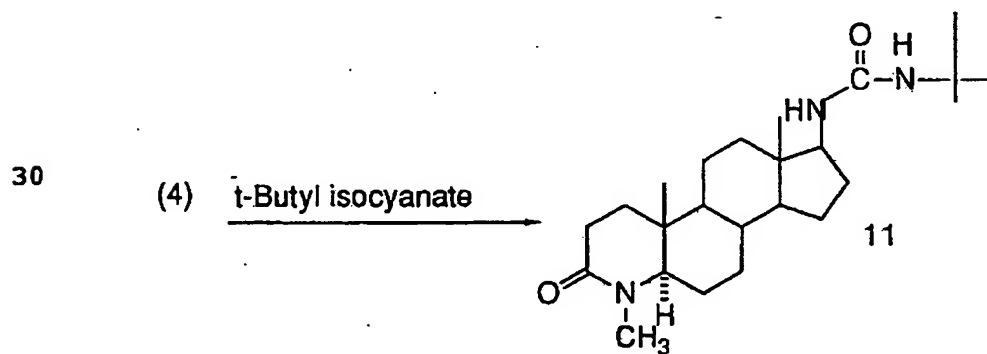
FLOWSHEET XVII

Ureas, thioureas, carbamates, and thiocarbamates

20 claimed in the present invention may readily be obtained by following the basic procedure(s) described in flowsheets XVI and XVII. To further illustrate, compound 2 may be replaced by the

amine (4) and reacted with t-butylisocyanate to yield 17-(N'-t-butylureido)-4-methyl-5 α -4-azaandrostane-3-one (11) (flowsheet

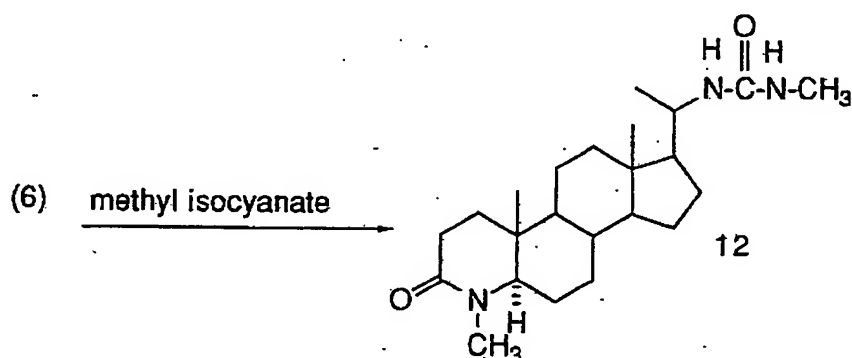
25 XVIII).



FLOWSHEET XVIII

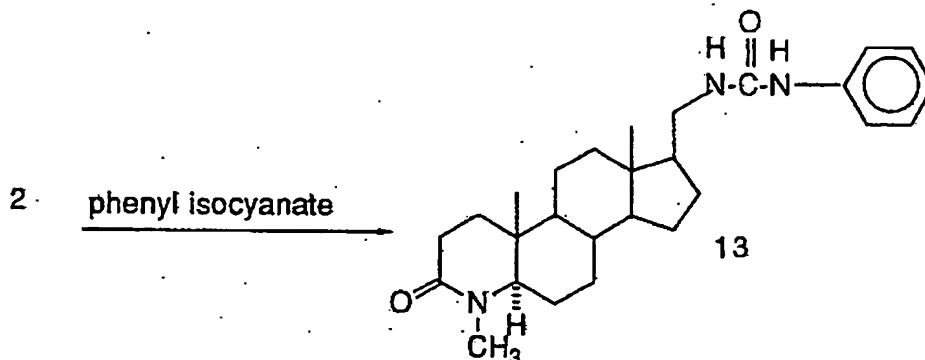
- 174 -

If compound 6 is reacted with methyl isocyanate under the conditions described for flowsheet XVI, 4-methyl-20-(N'-methyl-ureido)-5 α -4-azapregnan-3-one is obtained (2) (flowsheet XIX)



FLOWSHEET XIX

If compound 2 is reacted with phenyl isocyanate under the conditions described in flowsheet 16, 4-methyl-17-(N'-phenyl-uriedomethyl)-5 α -4-azaandrostane-3-one is made (13) (flowsheet XX).



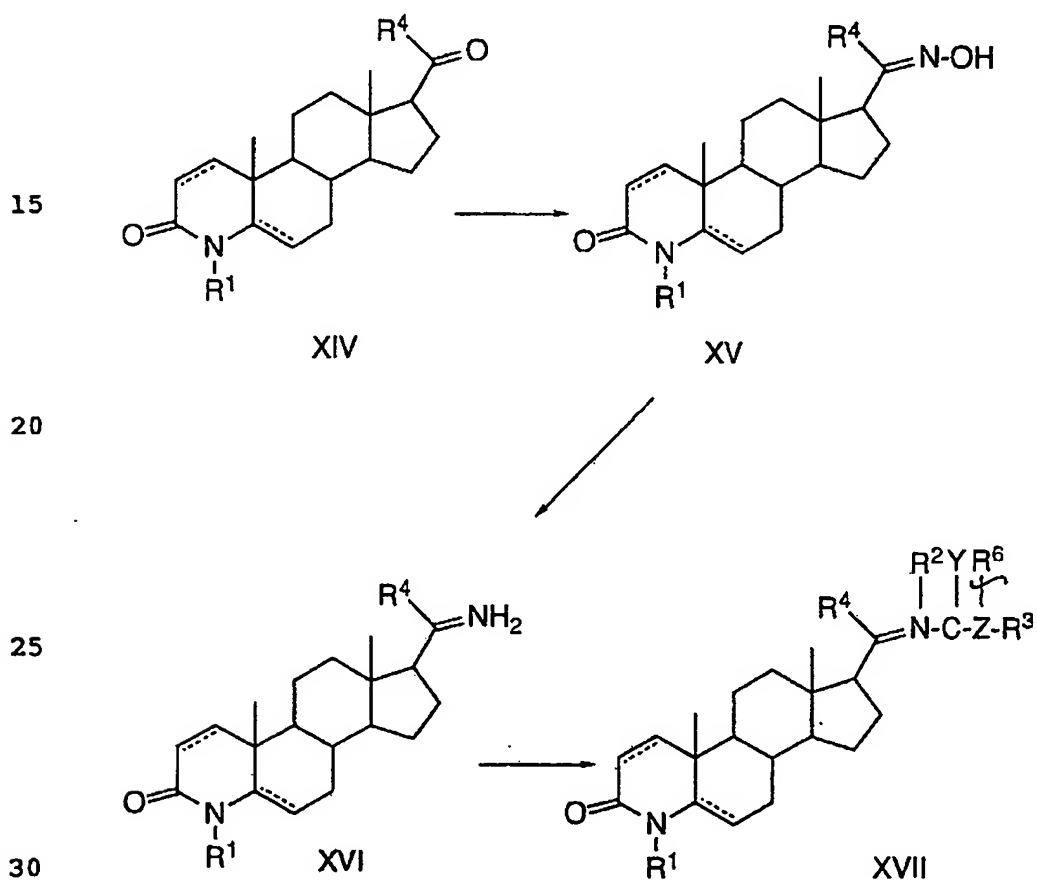
FLOWSHEET XX

In addition, dehydrogenation of the 1,2 position may readily be accomplished by known synthetic methodology to produce

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the claimed 1-en derivatives. See U.S. 5,061,802 and Dolling et al., J. Am. Chem. Soc., 110, 3318-19 (1988).

Flowsheets XXI, XXII and XXIII further illustrate how compounds claimed in the instant invention may be prepared. In flowsheet XXI, the starting 4-azasteroid aldehyde or ketone (XIV), obtained by known synthetic methods, is reacted to form the oxime XV; reduced to the amine XVI and reacted with a substituted isocyanate, substituted thioisocyanate, activated ester or thioester to form XVII.

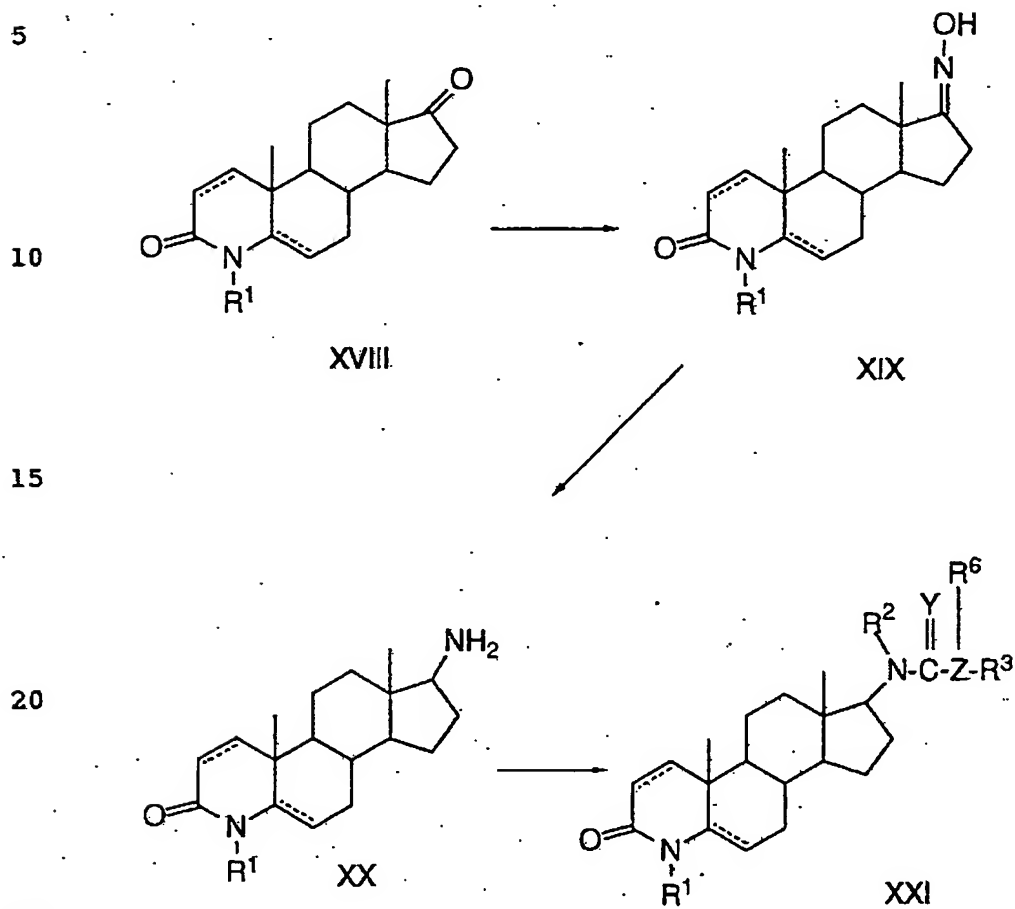


FLOWSHEET XX

In flowsheet XXII, the identical procedure is followed using a generic 4-azasteroid (XVIII), prepared by known synthetic

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methods, to produce the oxime (XIX) which is reduced to the amine XX and reacted with a substituted isocyanate, substituted thioisocyanate, activated ester or thioester to form XXI.

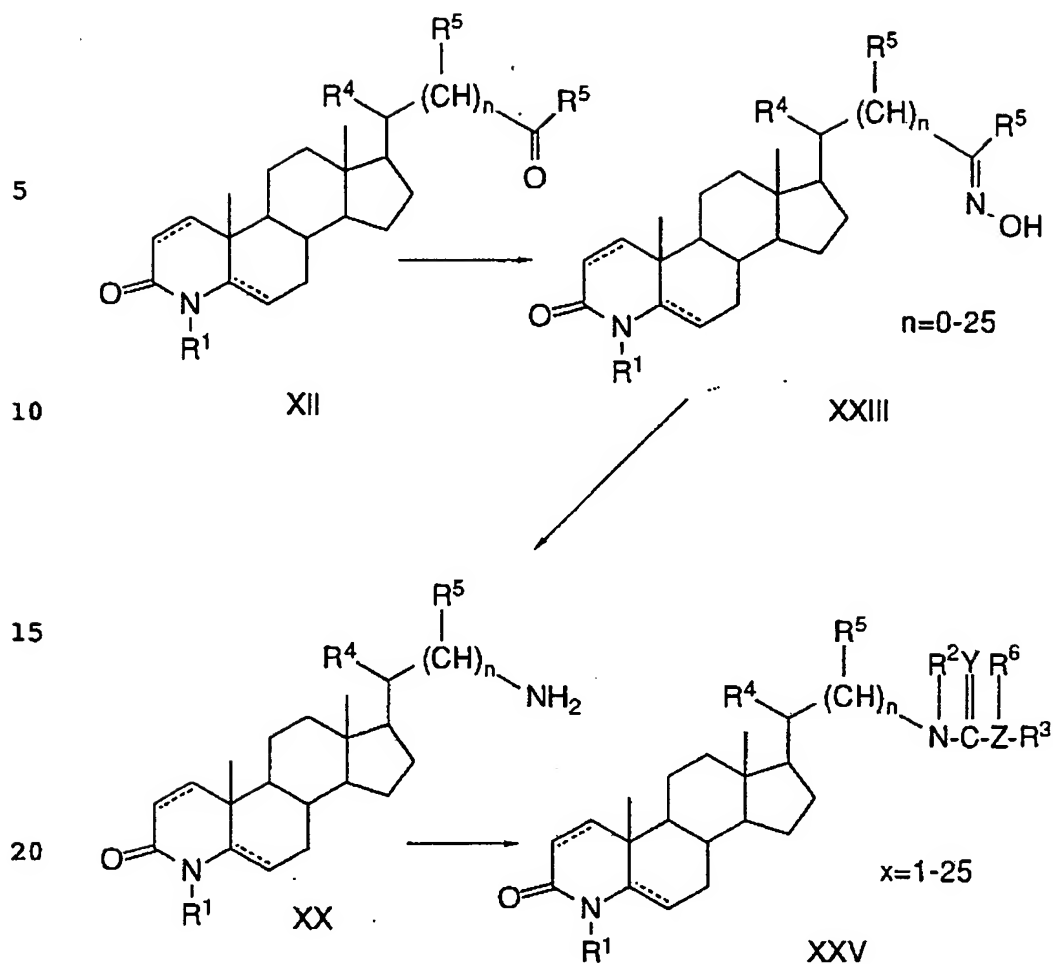


FLOWSHEET XXII

In flowsheet XXIII, the generic 4-azasteroid XXII, also obtained from well known synthetic methodology, is reacted to form the oxime XXIII, which is further reduced to the amine XXIV, and reacted with a substituted isocyanate, substituted thioisocyanate, activated ester or thioester to form XXV.

30

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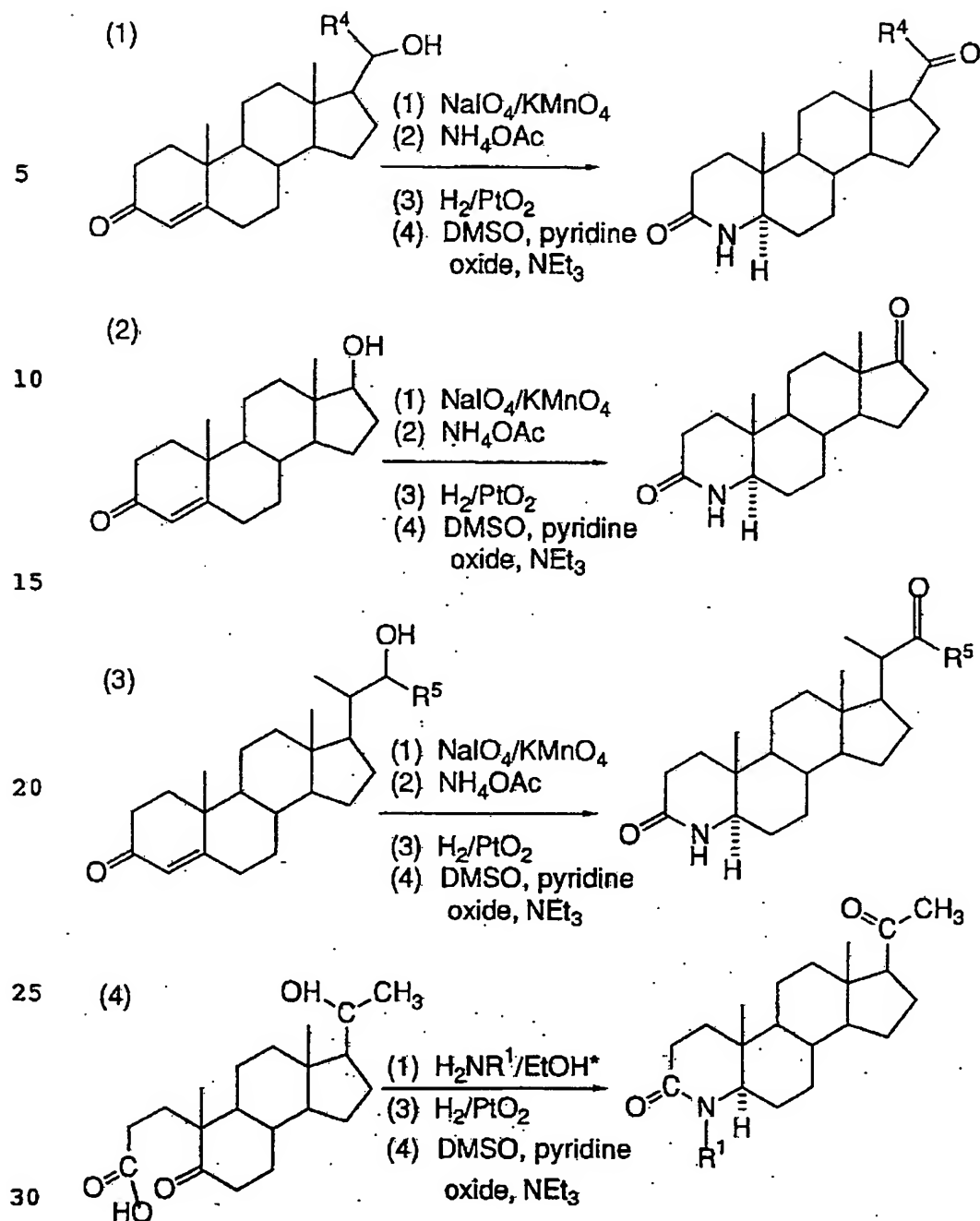
FLWSHEET XXIII

25

The starting 4-azasteroidal ketones used in the present invention may be prepared according to the basic procedures described in flowsheet XXIV via well known synthetic methodology.

30

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* U.S. Pat. No. 4,377,584

FLWSHEET XXIV

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The following examples further describe the synthesis of compounds claimed in the instant invention.

Synthesis of Starting 4-Azasteroid Oximes

5

EXAMPLE 46

46) 4-Methyl-3-oxo-5 α -4-azaandrostan-17-carboxaldehyde oxime

10 A stirred mixture of 4-methyl-3-oxo-5 α -4-aza-androstan-17-carboxaldehyde (0.952 g, 3.0 mM), hydroxylamine hydrochloride (1.10 g, 15.8 mM), anhydrous pyridine (6 mL) and anhydrous ethanol (12 mL) was refluxed gently under a nitrogen atmosphere for 6.3 hours. After cooling, the ice-cooled mixture was diluted, with stirring, with a slight excess of chilled dilute
15 hydrochloric acid (ca. 0.3 N), the suspension aged for ca. 20 minutes, filtered, washed with water and dried to give (1) 0.855 g. MS M⁺ calcd for C₂₀H₃₂N₂O₂ 332.48, observed m/e 332.

20 Synthesis of Reactant 4-Azasteroid Amines:

EXAMPLES 47-54

47) 17-Aminomethyl-4-methyl-5 α -4-azaandrostan-3-one

25 A mixture of (46) (0.67 g, 2.0 mM), ethanol (100 mL), glacial acetic acid (8 mL) and water (4 mL) was reduced in a hydrogen atmosphere (40 p.s.i.) at room temperature in the presence of PtO₂ until TLC analysis indicated complete reduction. The filtered reaction mixture was concentrated in vacuo, the residue taken up in chloroform, and the chloroform solution washed with
30 fresh dilute sodium hydrogen carbonate solution and dried (Na₂SO₄). Concentration of the filtered chloroform solution followed by trituration of the residue obtained with hexane containing a small amount of ether yielded (47) as an off-white solid. MS MH⁺ calcd for C₂₀H₃₄N₂O 318.49, observed m/e 319.

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The following amines are representative of those obtained from the corresponding carbonyl compounds utilizing the above procedures:

- 48) 17-Aminomethyl-5 α -4-azaandrostan-3-one.
- 5 49) 17-Amino-4-methyl-5 α -4-azaandrostane-3-one.
- 50) 17-Amino-5 α -4-azaandrostan-3-one.
- 51) 20-Amino-4-methyl-5 α -4-azapregnan-3-one.
- 52) 20-Amino-5 α -4-azapregnan-3-one.
- 53) 20-(Aminomethyl)-4-methyl-5 α -4-azapregnan-3-one.
- 10 54) 20-(Aminomethyl)-5 α -4-azapregnan-3-one.

Synthesis of Ureido 4-Azasteroid

EXAMPLES 55-58

15

55) 17-(N'-t-Butylureidomethyl)-4-methyl-5 α -4-azaandrostan-3-one

To a stirred solution of (47) (0.064 g, 0.2 mM) in dry benzene (8 mL) at room temperature was added t-butyl isocyanate (0.035 mL, 0.3 mM) dropwise over ca. 0.5 min. After stirring
20 overnight the benzene was removed in vacuo and the residue flash chromatographed (silica gel, ethyl acetate as eluant) to give (55) as a white solid. MS M⁺ calcd for C₂₅H₄₃N₃O₂ 417.64, observed m/e 417.

25

56) 17-(N'-t-Butylureido)-4-methyl-5 α -4-azaandrostan-3-one

When (2) in the above example was replaced by (49), (56) was obtained as a white solid. MS M⁺ calcd for C₂₄H₄₁N₃O₂ 403.61, observed m/e 405.

30

57) 4-Methyl-20-(N'-methylureido)-5 α -4-azapregnan-3-one

When (51) was reacted with methyl isocyanate under the conditions of Example (55), (57) was obtained as a white waxy solid. MS M⁺ calcd for C₂₃H₃₉N₃O₂ 389.58, observed m/e 389.

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58) 4-Methyl-17-(N'-phenylureidomethyl)-5 α -4-azaandrostan-3-one

When (47) was reacted with phenyl isocyanate under the conditions of Example (55), (58) was obtained as a white solid. MS MH⁺ calcd for C₂₇H₃₉N₃O₂ 437.40, observed m/e 438.

5

Examples 59-66 were prepared according to the basic procedures described above further exemplify the claimed invention.

59) 4-Methyl-17B-(N'-n-propylureidomethyl)-5 α -4-azaandro stan-3-one. MS MH⁺ calc. for C₂₄H₄₁N₃O₂ 403.40, observed m/e 404.

10

60) 4-Methyl-17B-(N'-n-octylureidomethyl)-5 α -4- azaandro stan-3-one. MS MH⁺ calc. for C₂₉H₅₁N₃O₂ 473.49, observed m/e 474.

15

61) 4-Methyl-17B-(N'-phenylureido)-5 α -4-azaandro stan-3-one. MS MH⁺ calc. for C₂₆H₃₇N₃O₂ 423.52, observed m/e 424.

62) 17B-(N'-Isopropylureidomethyl)-4-methyl-5 α -4- aza-androstan-3-one. MS MH⁺ calcd for C₂₄H₄₁N₃O₂ 403.61 observed m/e 404.

20

63) 20-(N'-t-Butylureidomethyl)-4-methyl-5 α -4-aza-pregnan-3-one. MS MH⁺ calcd for C₂₇H₄₇N₃O₂ 445.35, observed m/3 446.

25

64) 20-((Iminodibenz-5-yl)carbonylaminomethyl)-4-methyl-5 α -4-azapregnan-3-one. MS MH₂⁺⁺ calcd. for C₃₇H₄₉N₃O₂ 567.82, observed m/e 569.

30

65) 17B-((Iminodibenz-5-yl)carbonylaminomethyl)-4-methyl-5 α -4-azaandrostan-3-one. MS MH₂⁺⁺ calcd.for C₃₅H₄₅N₃O₂ 539.74, observed m/e 541.

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66) 17 β -((Isobutyloxycarbonylaminomethyl)-4-methyl-5 α -4-azaandrostan-3-one. MS MH⁺ calcd. for C₂₅H₄₂N₂O₃ 418.62, observed m/e 419.

5

TABLE 4
NMR DATA (PPM)

	<u>Example</u>	<u>Angular Methyls</u>	<u>Miscellaneous</u>
10	55	0.66, 0.86	1.33 (-NHCONH-C(CH ₃) ₃)
	56	0.67, 0.88	1.33 (-NHCONH-C(CH ₃) ₃)
	57	0.73, 0.88	2.92 (-4-NCH ₃)
	58	0.64, 0.86	2.92 (-4-NCH ₃)
	59	0.64, 0.88	2.90 (-4-NCH ₃)
15	60	0.65, 0.88	2.92 (-4-NCH ₃)
	61	0.63, 0.86	2.93 (-4-NCH ₃)
	62	0.66, 0.88	1.12 (-NH-CH(CH ₃) ₂)
			1.16
	63	0.64, 0.85	1.29 (-NHCONH-C(CH ₃) ₃)
20	64	0.62, 0.89	0.82 -CH(CH ₃)CH ₂ NHCON-
			0.86
	65	0.61, 0.88	2.92 (-4-NCH ₃)
	66	0.66, 0.88	2.92 (-4-NCH ₃)

25

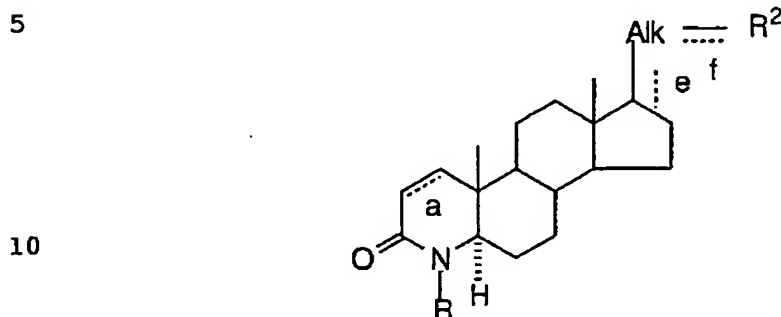
The above examples are non-limiting and suitable acylating agents, isocyanates, or thioisocyanates may readily be substituted according to the methods described in the present invention and reacted with a described azasteroidal amine to form the claimed ureas, thioureas, carbamates, and thiocarbamates. The following definitions further clarify the present invention.

30

EXAMPLES FOR THE CASE WHEN SUBSTITUENT "A" OF
GENERAL FORMULA "I" IS AS DEFINED IN GROUP "VII(A)"

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Further provided are novel 17 β -substituted olefinic and saturated 4-aza-5 α -androstan-3-one and related compounds of the general structural formula XVII:



wherein:

Alk is C₁-C₄ straight or branched chain alkyl or alkenyl;

15 dashed lines a, e and f each can independently represent a double bond when present, with the proviso that double bonds formed by e and f are not both present concurrently;

20 R is selected from hydrogen, methyl or ethyl;

R² is (a) C₆-C₁₀ aryl, cyano, a 5-6 membered heteroaryl radical, which can contain 1-4 nitrogen atom, one oxygen or sulfur atoms or combinations thereof with 1-2 nitrogen atoms, providing that where R² is cyano, double bonds e and f are not present;

25

(b) COR₁, where R₁ is C₆-C₁₀ aryl, substituted C₆-C₁₀ aryl, and heteroaryl;

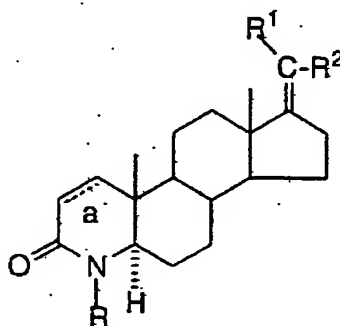
30 (c) CONHR₂, where R₂ is substituted phenyl, heteroaryl, substituted heteroaryl, or C₇ to C₁₂ cycloalkyl;

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(d) CO_2R_3 , where R_3 is C_1 - C_{18} linear or branched alkyl, C_6 - C_{10} aryl, substituted C_6 - C_{10} aryl, or C_7 - C_{12} cycloalkyl; providing that in (b), (c) or (d), Alk is only alkenyl;

wherein the above aryl or heteroaryl radicals can also be fused with a benzo or another heteroaryl ring and can further be substituted with one or more substituents; and pharmaceutically acceptable salts and esters thereof.

Further provided is a compound of the general structural formula XVIII:



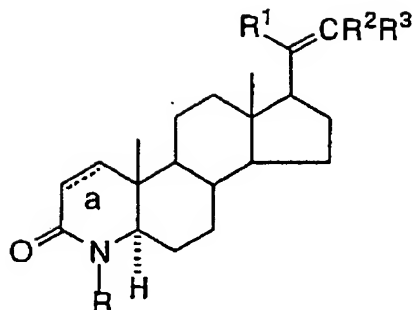
wherein

the dashed line a represents a double bond when present, R and R^1 are selected from hydrogen, methyl and ethyl; and

R^2 is as defined above, including both (E) and (Z) forms, and mixtures thereof.

Also provided is a compound of the general structural formula XIX:

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5

10 wherein

the dashed line a can represent a double bond when present,
 R , R^1 and R^3 are

independently selected from hydrogen, methyl and ethyl, with the
 proviso that at least one of R^1 and R^3 is hydrogen,

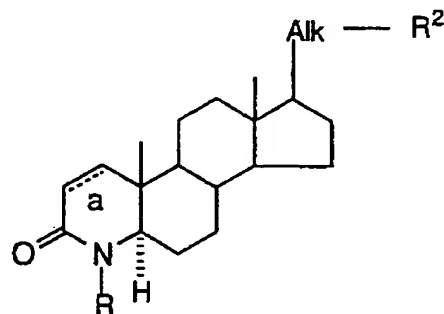
15

R^2 is C_6-C_{10} aryl or heteroaryl as defined above, and R^2

and R^3 can be in a E or Z bond configuration, and mixtures
 thereof.

20

Additionally, there is provided a compound of the
 general structural formula XX:



25

30

wherein:

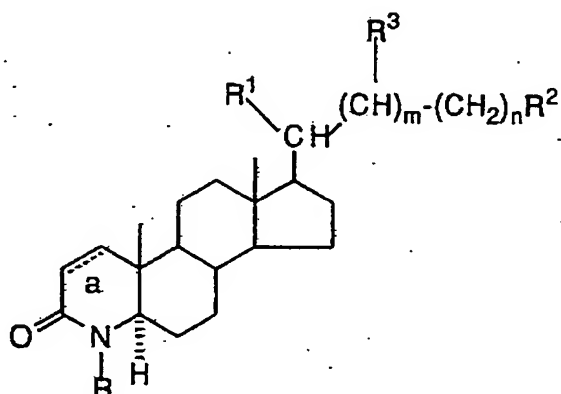
Alk is C_1-C_4 straight or branched chain alkyl; dashed line a
 can represent a double bond when present;

R is selected from hydrogen, methyl or ethyl; and

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R^2 is as defined above.

Also specifically provided is a compound of general structural formula XXI:



wherein:

the dashed line a can represent a double bond when present, and m is 0-1, n is 0-3; and

R, R^1 and R^3 are

independently selected from hydrogen, methyl and ethyl, with the proviso that at least one of R^1 and R^3 is hydrogen,

R^2 is C_6 - C_{10} aryl, cyano, or heteroaryl as defined above.

The structures XVII through XXI above encompass starting 5α -reductase inhibitor compounds of this invention.

Where the double bond "e" is present, the compounds are delta-17 olefins and where the double bond "f" is present, the compounds are delta-20 olefins. Note that dashed lines "e" and "f" both cannot be double bonds concurrently.

Dashed line "a" can independently be a double bond and when present, the compound is a delta-1-ene.

R^2 is a C_6 - C_{10} aryl including phenyl, benzyl, 1- and 2-phenethyl and naphthyl, and also cyano.

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Preferred is where R^2 aryl is phenyl or cyano.

R^2 can also be 5-6 membered heteroaryl radical being fully unsaturated containing 1-4 nitrogen atoms, e.g. pyridyl, pyrrol, imidazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, pyrazolyl, or triazolyl; containing 1-2 oxygen or sulfur atoms, e.g. thienyl, furanyl; or in combination with 1-2 nitrogen atoms, e.g. isothiazolyl, thiazolyl, isoxazolyl, oxazolyl or thiadiazolyl; or fused with a benzo ring, e.g. quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, indolyl, carbazolyl; or fused with another heteroaryl ring, e.g. purinyl, and the like.

Preferred examples are 2-, 3-, and 4-pyridyl, 2-thienyl; 2-pyrazinyl, 2-, 4-, and 5-thiazolyl.

The R^2 aryl or heteroaryl ring can be unsubstituted or substituted with one or more of the following substituents providing the substitution leads to a chemically inert, but biologically active 5α reductase inhibitor.

The R^2 ring substituents include:

C_1 - C_8 straight or branched alkyl; e.g. methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, n-hexyl, iso-hexyl, n-butyl, n-octyl, iso-octyl, t-octyl, and the like; C_2 - C_8 straight or branched alkenyl, e.g. ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 1-hexenyl, 1-heptenyl, 1-octenyl, 2-octenyl, and the like;

C_3 - C_8 cycloalkyl e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methyl-cyclobutyl, cyclopentyl, cyclohexyl, 1-methyl-cyclohexyl, 2-methylcyclohexyl, 2-ethylcyclohexyl, and the like;

C_2 - C_8 alkynyl e.g., 1-ethynyl; 1-propynyl, 2-propynyl, 2-butylnyl, 2-pentylnyl, 1-hexynyl, 1-heptynyl, 1-octynyl;

$CONR^4R^5$ where R^4 and R^5 independently are H, C_1 - C_8 alkyl, as defined above, C_3 - C_8 cycloalkyl as defined above, C_1 - C_4 perhaloalkyl e.g., trifluoromethyl, perfluoromethyl, trichloromethyl, preferably perfluoroalkyl; phenyl, or substituted phenyl, as described below;

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COR⁴, where R⁴ is defined above, including acetyl, isobutylcarbonyl, benzoyl and the like;

S(O)_n R⁴, where n is 0-2 and R⁴ is defined above, including methylsulfinyl, methylsulfonyl, phenylsulfonyl, 4-chlorophenylsulfinyl and the like;

OCOR⁴, where R⁴ is defined above, including acetoxy, propionyloxy, benzoyloxy, 4-chlorobenzoyloxy and the like.

SO₂NR⁴R⁵ where R⁴ and R⁵ are described above, including sulfonamido, N-methylsulfonamido, N-phenylsulfonamido, N,N-dimethylsulfonamido and the like;

NR⁴(CO)R⁵, wherein R⁴ and R⁵ are defined above, including; acetylamino, benzoylamino, N-methylbenzoylamino and the like;

NR⁴(CO)NHR⁵, wherein R⁴ and R⁵ are described above, including; ureido, N-methylureido, N-methyl-N¹-phenylureido and the like;

NHSO₂R⁴, R⁴ being defined above, including methylsulfonylamino, phenylsulfonylamino and the like;

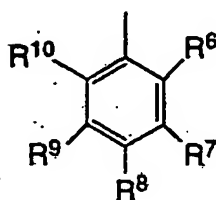
OR⁴, where R⁴ is defined above, including methoxy, phenoxy, 4-chlorophenoxy and the like.

NR⁴R⁵, wherein R⁴ and R⁵ are described above, including amino, methylamino, dimethylamino, anilino and the like;

Cyano, nitro, halo, including: fluoro, chloro, bromo and iodo;

Perhalo C₁-C₄ alkyl, including: trifluoromethyl, perfluoroethyl, trichloromethyl and the like.

CO₂R⁴, wherein R⁴ is defined above, including CO₂CH₃, CO₂Ph, CO₂-(1-adamantyl) and the like; phenyl and substituted phenyl of the formula:



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wherein the radicals R⁶-R¹⁰ each can represent one or more of the substituents defined above, including; hydrogen, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 4-phenoxy and the like.

5 Representative compounds of the present invention include the following:

- (17E)-17-[phenyl)methylene]-4-methyl-4-aza-5 α -androstan-3-one,
10 (17E)-17-[(4-chlorophenyl)methylene]-4-methyl-4-aza-5 α -androstan-3-one,
 (17E)-17-[(3-chlorophenyl)methylene]-4-methyl-4-aza-5 α -androstan-3-one,
 (17E)-17-[(2-chlorophenyl)methylene]-4-methyl-4-aza-5 α -androstan-3-one,
15 (17E)-17-[(4-ethoxycarbonylphenyl)methyl-ene]-4-methyl-4-aza-5 α -androstan-one,
 (17E)-17-[(4-carboxyphenyl)methylene]-4-methyl-4-aza-5 α -androstan-3-one,
20 (17E)-17-[4-[(1,1-dimethylethyl)amino)-carbonyl]phenyl]-methylene]-4-methyl-4-aza-5 α -androstan-3-one,
 (17E)-17-[(3,4,5-trimethoxyphenyl)methyl-ene]-4-aza-5 α -androstan-3-one,
 (17E)-17-[(2-methoxyphenyl)methylene]-4-methyl-4-aza-5 α -androstan-3-one,
25 (17E)-17-[(4-methylsulfonylphenyl)methyl-ene]-4-methyl-4-aza-5 α -androstan-3-one,
 (17E)-17-[(4-biphenyl)methylene]-4-aza-5 α -androstan-3-one,
 (17E)-17-[(4-nitrophenyl)methylene]-4-methyl-4-aza-5 α -androstan-3-one,
30 (17E)-17-[(4-aminophenyl)methylene]-4-aza-5 α -androstan-3-one,
 (17E)-17-[(4-acetylaminophenyl)methylene]-4-methyl-4-aza-5 α -androstan-3-one,

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- (17E)-17-(4-pivaloylaminophenyl)methylene)-4-methyl-4-aza-5 α -androst-3-one,
(17E)-17-[(4-phenoxyphenyl)methylene]-4-aza-5 α -androst-3-one,
5 (17E)-17-[(2-imidazolyl)methylene]-4-methyl-4-aza-5 α -androst-1-en-3-one,
(17E)-17-[(2-thiazolyl)methylene]-4-aza-5 α -androst-1-en-3-one,
(17E)-17-[(2-pyrazinyl)methylene]-4-methyl-4-aza-5 α -androst-3-one,
10 (17E)-20-phenyl-4-methyl-4-aza-5 α -pregn-17-en-3-one,
(17E)-20-[(4-chloro)phenyl]-4-aza-5 α -pregn-17-en-3-one,
(20E)-4-methyl-21-[(4-methoxy)phenyl]-4-aza-5 α -pregn-20-en-3-one,
(20E)-4-methyl-21-phenyl-4-aza-5 α -pregn-20-en-3-one,
15 (20E)-4-methyl-21-[(4-methyl)phenyl]-4-aza-5 α -pregn-20-en-3-one,
(20E)-4-methyl-21-[(4-chloro)phenyl]-4-aza-5 α -pregn-20-en-3-one,
(20E)-4-methyl-21-(4-pyridyl)-4-aza-5 α -pregn-20-en-3-one,
20 (20E)-4-methyl-21-[(3-chloro)phenyl]-4-aza-5 α -pregn-20-en-3-one,
(20E)-4-methyl-21-[(2-chloro)phenyl]-4-aza-5 α -pregn-20-en-3-one,
(20E)-4-methyl-21-(2-pyridyl)-4-aza-5 α -pregn-20-en-3-one,
25 (20E)-4-methyl-21-(2-thienyl)-4-aza-5 α -pregn-20-en-3-one,
(20E)-21-[(4-methoxy)phenyl]-4-aza-5 α -pregn-20-en-3-one,
(20E)-4-methyl-21-(3-thienyl)-4-aza-5 α -pregn-20-en-3-one,
(20E)-4-methyl-21-(2-furanyl)-4-aza-5 α -pregn-20-en-3-one,
30 (20E)-4-methyl-21-[(2-fluoro)phenyl]-4-aza-5 α -pregn-20-en-3-one,
(20E)-21-(4-pyridyl)-4-aza-5 α -pregn-1,20-dien-3-one,
(20E)-21-(4-pyridyl)-4-aza-5 α -pregn-20-en-3-one,
(20E)-21-[(4-methoxy)phenyl]-4-aza-5 α -pregn-1,20-dien-3-one,
(20E)-21-(2-furanyl)-4-aza-5 α -pregn-1,20-dien-3-one,

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- (20E)-21-(2-pyridyl)-4-aza-5 α -pregn-1,20-dien-3-one,
(20E)-21-(3-pyridyl)-4-aza-5 α -pregn-1,20-dien-3-one
(20E)-21-[(4-ethoxycarbonyl)-phenyl]-4-aza-5 α -pregn-1,20-dien-
3-one,
5 (20E)-21-4-[N-phenyl]benzamido-4-aza-5 α -pregn-1,20-dien-3-
one,
(20E)-21-(2-pyridyl)-4-aza-5 α -pregn-20-en-3-one,
(20E)-21-(3-pyridyl)-4-aza-5 α -pregn-20-en-3-one,
(20E)-21-(2-thienyl)-4-aza-5 α -pregn-20-en-3-one,
10 (20E)-4,20-dimethyl-21-phenyl-4-aza-5 α -pregn-20-en-3-one,
(20E)-4,20-dimethyl-21-(4-chlorophenyl)-4-aza-5 α -pregn-20-en-
3-one,
(20E)-4,20-dimethyl-21-(2-thienyl)-4-aza-5 α -pregn-20-en-3-one,
(20E)-4,20-dimethyl-21-(2-pyridyl)-4-aza-5 α -pregn-20-en-3-one,
15 (20E)-20-methyl-21-(4-pyridyl)-4-aza-5 α -pregna-1,20-dien-3-
one,
(20E)-4,20-dimethyl-21-(4-pyridyl)-4-aza-5 α -pregn-20-en-3-one,
(20E)-20-methyl-21-(2-furyl)-4-aza-5 α -pregna-1,20-dien-3-one,
(20E)-20-methyl-21-(2-pyridyl)-4-aza-5 α -pregna-1,20-dien-3-
20 one,
(20E)-20-ethyl-21-phenyl-4-aza-5 α -pregna-1,20-dien-3-one,
(20E)-20-ethyl-21-(2-pyridyl)-4-aza-5 α -pregna-1,20-dien-3-one,
20(E,Z)-4,21-dimethyl-21-phenyl-4-aza-5 α -pregn-20-en-3-one,
20(E,Z)-21-methyl-21-(4-chlorophenyl)-4-aza-5 α -pregn-20-en-3-
25 one,
20(E,Z)-4,21-dimethyl-21-(2-pyridyl)-4-aza-5 α -pregn-1,20-dien-
3-one,
17 β -[(4-chlorophenyl)methyl]-4-methyl-4-aza-5 α -androstan-3-
one,
30 17 β -[(phenyl)methyl]-4-aza-5 α -androstan-3-one,
17 β -[(2-pyridyl)methyl]-4-methyl-4-aza-5 α -androst-1-en-3-one,
17 β -[(2-thienyl)methyl]-4-aza-5 α -androst-1-en-3-one,
20-phenyl-4-methyl-4-aza-5 α -pregnan-3-one,
20-(4-chloro)phenyl-4-aza-5 α -pregnan-3-one,

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- 20-(2-pyridyl)-4-methyl-4-aza-5 α -pregn-1-en-3-one,
20-(2-thienyl)-4-aza-5 α -pregn-1-en-3-one,
21-phenyl-4-aza-5 α -pregnan-3-one,
21-(2-pyridyl)-4-methyl-4-aza-5 α -pregnan-3-one,
5 21-[(4-methoxy)phenyl]-4-methyl-4-aza-5 α -pregnan-3-one,
21-(2-thienyl)-4-methyl-4-aza-5 α -pregnan-3-one,
21-[(4-chlorophenyl)-4-aza-5 α -pregn-1-en-3-one,
4-methyl-17 β -[3-(phenyl)propyl]-4-aza-5 α -androst-1-en-3-one,
17 β -[3-(2-pyridyl)propyl]-4-aza-5 α -androst-1-en-3-one,
10 17 β -[3-(4-chlorophenyl)propyl]-4-aza-5 α -androst-1-en-3-one,
4-methyl-17 β -[2-(thienyl)propyl]-4-aza-5 α -androst-1-en-3-one,
4-methyl-17 β -[4-(phenyl)butyl]-4-aza-5 α -androst-1-en-3-one,
17 β -[3-(2-pyridyl)butyl]-4-aza-5 α -androst-1-en-3-one,
17 β -[3-(4-chlorophenyl)butyl]-4-aza-5 α -androst-1-en-3-one,
15 4-methyl-17 β -[2-(thienyl)butyl]-4-aza-5 α -androst-1-en-3-one,
20-ethyl-21-(2-pyridyl)-4-aza-5 α -pregnan-3-one,
20-ethyl-21-phenyl-4-aza-5 α -pregnan-3-one,
20-ethyl-21-(2-methoxyphenyl)-4-aza-5 α -pregnan-3-one,
4,21-dimethyl-21-(2-pyridyl)-4-aza-5 α -pregnan-3-one,
20 4,21-dimethyl-21-[(4-benzoylamino)phenyl]-4-aza-5 α -pregnan-3-one,
4,21-dimethyl-21-(2-thiazolyl)-4-aza-5 α -pregnan-3-one,
21-phenyl-4-aza-5 α -pregnan-3-one,
21-(2-pyridyl)-4-aza-5 α -pregnan-3-one,
25 21-(2-thienyl)-4-aza-5 α -pregnan-3-one,
21-(2-methoxyphenyl)-4-aza-5 α -pregn-1-en-3-one,
21-(3-pyridyl)-4-aza-5 α -pregn-1-en-3-one,
21-(2-thiazolyl)-4-aza-5 α -pregn-1-en-3-one,
4-methyl-21-[4-(methylsulfonyl)phenyl]-4-aza-5 α -pregn-1-en-3-one,
30 one,
4-ethyl-21-(4-fluorophenyl)-4-aza-5 α -pregn-1-en-3-one,
4-methyl-21-(4-carboxyphenyl)-4-aza-5 α -pregn-1,20-dien-3-one,
4-ethyl-21-(4-carbamoylphenyl)-4-aza-5 α -pregn-1,20-dien-3-one,
20-(3-pyridyl)-4-aza-5 α -pregna-1,17-dien-3-one,

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- 4-methyl-20-(2-pyrazinyl)-4-aza-5 α -pregn-1,17-dien-3-one,
20-ethyl-4-methyl-21-phenyl-4-aza-5 α -pregn-20-en-3-one,
4,20-dimethyl-21-(2,6-dimethoxyphenyl)-4-aza-5 α -pregna-1,20-
dien-3-one,
5 20-ethyl-4-methyl-21-(s-triazinyl)-4-aza-5 α -pregna-1,20-dien-3-
one,
4-methyl-20-(phenylmethyl)-4-aza-5 α -pregnan-3-one,
20-ethyl-4-methyl-21-(2-pyridyl)-4-aza-5 α -pregnan-3-one,
20-(2-thiazolyl)-4-aza-5 α -pregnan-3-one,
10 20-ethyl-21-(3-pyridyl)-4-aza-5 α -pregnan-3-one,
20-(4-methylsulfonylphenyl)-4-aza-5 α -pregn-1-en-3-one,
20-ethyl-21-(4-methoxyphenyl)-4-aza-5 α -pregn-1-en-3-one,
4-methyl-20-(3,4-dimethoxyphenyl)-4-aza-5 α -pregn-1-en-3-one,
20-ethyl-4-methyl-21-(2-pyrimidinyl)-4-aza-5 α -pregn-1-en-3-
15 one,
4,21-dimethyl-21-(4-pyridyl)-4-aza-5 α -pregna-1,20-dien-3-one,
21-methyl-21-(2-thienyl)-4-aza-5 α -pregn-1-en-3-one,
21-methyl-21-(1-imidazolyl)-4-aza-5 α -pregnan-3-one,
4,21-dimethyl-21-(4-carbamoylphenyl)-4-aza-5 α -pregn-1-en-3-
20 one,
4-methyl-21-(4-methoxyphenyl)-4-aza-5 α -pregnan-3-one,
4-methyl-17-((4-chloro)phenylmethyl)-4-aza-5 α -androstan-3-one,
N-(1,1-dimethylethyl)-4-(4-methyl-3-oxo-4-aza-5 α -pregn-21-
yl)benzamide,
25 4-methyl-21-(3-pyridyl)-4-aza-5 α -pregn-20-en-3-one,
21-(2-pyrazinyl)-4-methyl-4-aza-5 α -preg-20-en-3-one,
4-methyl-21-(2-pyrazinyl)-4-aza-5 α -pregnan-3-one,
4-methyl-24-nor-4-aza-5 α -cholane-23-nitrile,
4-methyl-3-oxo-4-aza-5 α -pregnane-21-carbon-nitrile,
30 24-nor-4-aza-5 α -chol-1-ene-23-nitrile,
24-nor-4-aza-5 α -cholane-23-nitrile,
4-methyl-24-nor-4-aza-5 α -chol-1-ene-23-nitrile,
3-oxo-4-aza-5 α -pregn-1-ene-21-carbonitrile,
3-oxo-4-aza-5 α -pregnane-21-carbonitrile,

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4-methyl-3-oxo-4-aza-5 α -pregnane-21-nitrile,
4-methyl-3-oxo-4-aza-5 α -cholane-24-nitrile,
3-oxo-4-aza-5 α -chol-1-ene-24-nitrile,
4-methyl-3-oxo-21-nor-4-aza-5 α -cholane-24-nitrile,
5 3-oxo-21-nor-4-aza-5 α -cholane-24-nitrile,

and also including the corresponding compounds wherein the 4-hydrogen substituent is replaced by a methyl or an ethyl radical, and/or a delta-one double bond is present.

10 Also included within the scope of this invention are pharmaceutically acceptable salts, i.e. hydrochloride, hydrobromide, acetate, pamoate, and the like, of the compound where a basic heteroaryl radical is present, e.g. 4-pyridyl, which can be used as the dosage form for modifying solubility or hydrolysis characteristics or
15 for use as sustained release or prodrug formulations.

The novel compounds of formula XVII of the present invention are prepared by methods starting with appropriate steroid 17-carboxaldehydes and ketones of the following formulae:

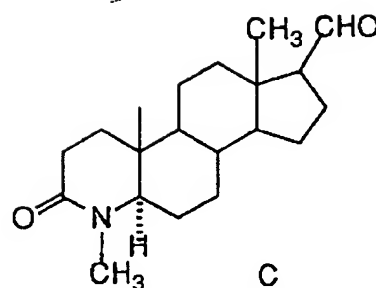
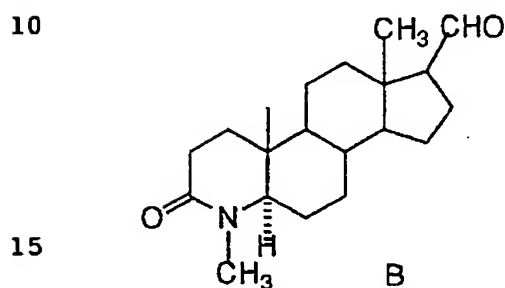
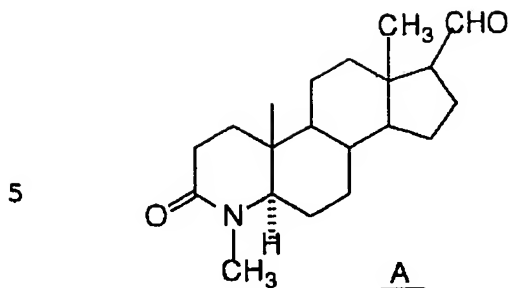
20 FLWSHEET XXV.

Carboxaldehydes

25

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20 Carboxaldehyde A can be prepared from 17-(2-pyridylthio) carboxylate-4-methyl-5 α -androstan-3-one by reaction with Raney nickel to the 17 β -carbinol followed by oxidation to the aldehyde with pyridinium chlorochromate. (See J. Med. Chem. 1986, Vol. 29, No. 11, p. 2299, Compound 10bg) The starting 2-pyridylthio ester can be made by hydrolyzing the 17-COOMe derivative to the acid and reacting the acid with 2,2'-dipyridyl disulfide in an inert solvent, e.g. chlorobenzene.

25 Carboxaldehyde B can be prepared from the lithium aluminum hydride reduction of 17 β -(N-methyl-N-methoxy)-carboxamide-5 α -4-aza-androst-1-en-3-one (see USP 5,061,801 for its preparation, as also described in the following section "Preparation of Starting Materials".

30 Carboxaldehyde C can be concurrently prepared from the same procedure, as a secondary reaction product, as described above for Carboxaldehyde B (See preparation in "Preparation of Starting Materials").

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Note that the corresponding 4-ethyl analogs are also available through conventional alkylation of the 4-NH derivative via, e.g. ethyl iodide, sodium hydride in dry DMF at room temperature.

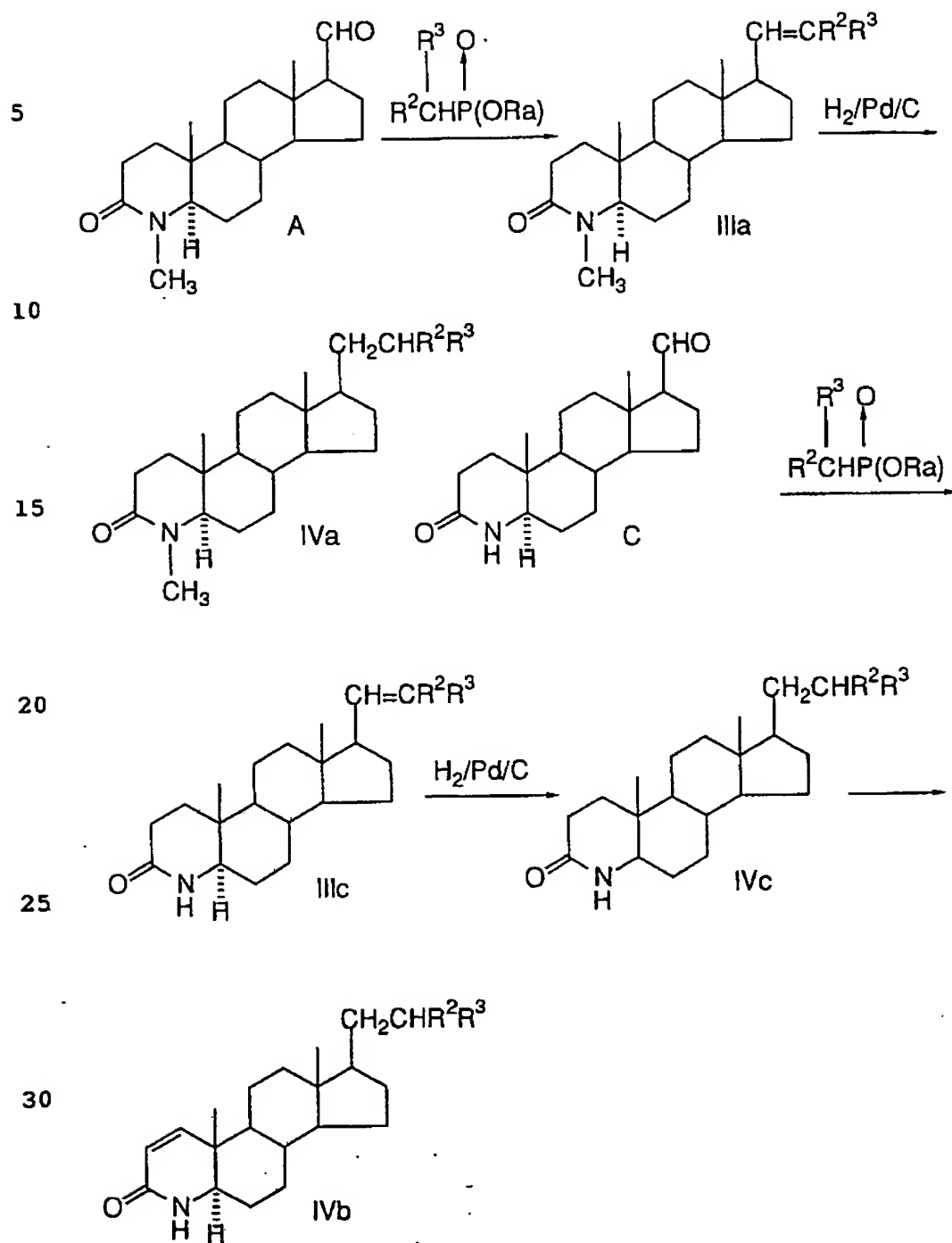
5 As seen in Flowsheet XXV, the carboxaldehydes A,B, or C can be reacted with the phosphonate reagent as shown, where R^2 is defined above, R^3 is hydrogen or methyl and R_a is a conventional ester alkyl radical, e.g. methyl or ethyl, to yield the corresponding D-20 olefins.

10 In general, the procedure for reacting the carboxaldehyde with the phosphonate ylid reagent is analogous to the conditions as described for the Wadsworth-Emmons modification of the Wittig reaction (See Chem. Rev. 74, p. 87, 1974 and JACS Vol. 83, p. 1733, 1961). The phosphonate ylid is reacted under
15 anhydrous conditions with the carboxaldehyde in about a 1:1 molar ratio together with a hydride reagent, e.g. sodium hydride, also in a 1:1 molar ratio with the phosphonate reagent in a dry solvent, e.g. dimethylformamide, dimethylacetamide, tetrahydrofuran, dioxane, DMSO and the like, under anhydrous conditions, usually a nitrogen
20 atmosphere, at a temperature of about 50-100°C, preferably 80-85°C for about 1-4 hours. Workup is conventional, e.g. organic liquid extraction followed by drying, evaporating off solvent, followed by chromatography, distillation or recrystallization of the crude material to yield the desired product, being a species of Formula
25 XVII.

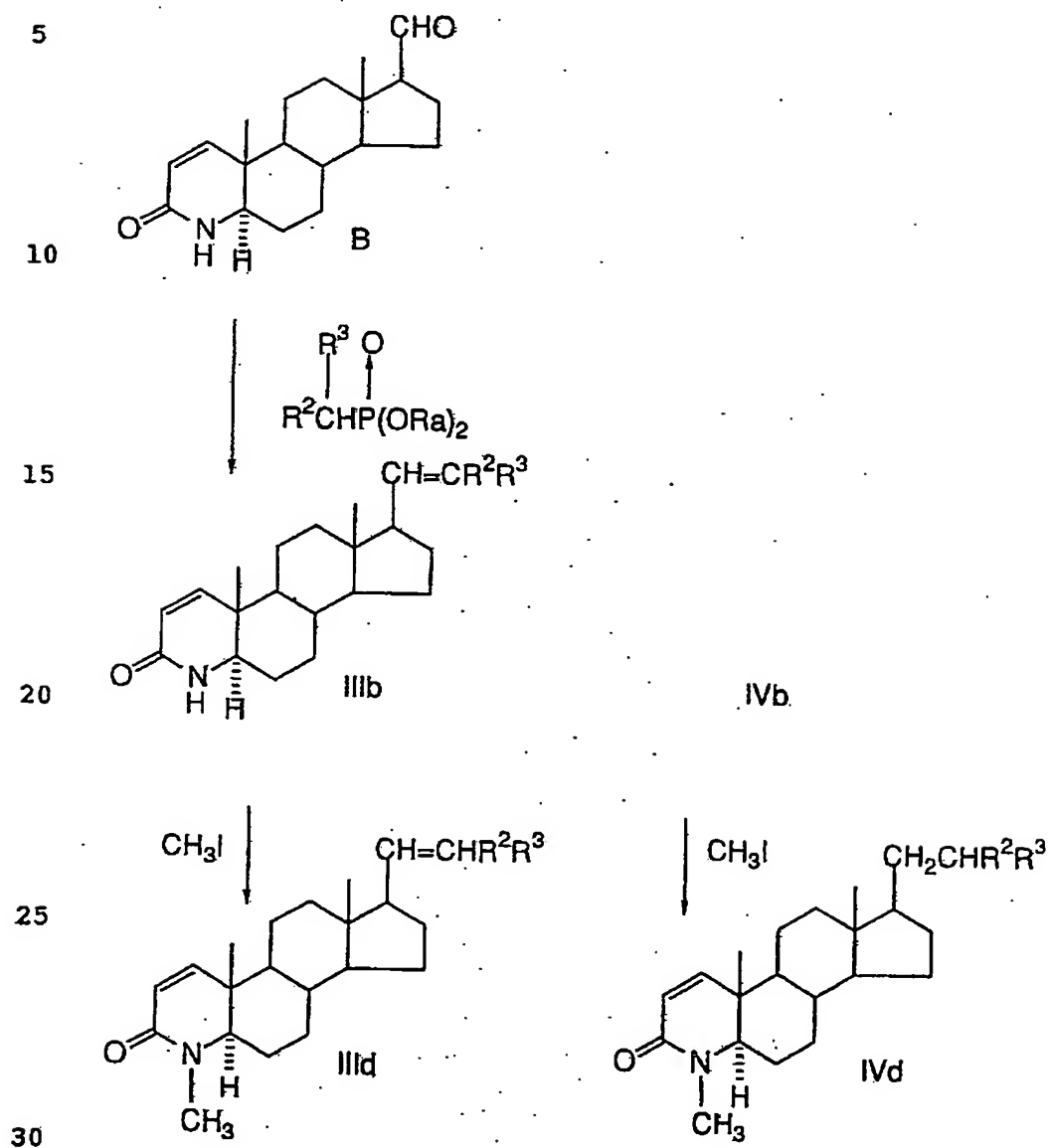
The starting phosphonates can be prepared by known procedures in the art. One procedure that can be used is the modified Arbuzov reaction in which a chloromethyl-aryl or
heteroaryl compound, e.g. thienylmethyl chloride, is reacted with an
30 alkyl phosphite, e.g. triethyl phosphite, at 125-175°C for 1-10 hours. Conventional workup yields the desired starting phosphonate, e.g. diethyl 2-thienylmethylphosphonate.

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FLOWSHEET XXVI



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FLWSHEET XXVI (CONT'D)

Alternately, the chloromethyl heteroaryl compound, e.g. 4-chloromethylpyridine, can be reacted with diethylphosphite and sodium hydride at about 80-100°C for several hours to also produce the desired phosphonate starting materials.

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Representative syntheses are given in the "Preparation of Starting Materials" section and representative examples of phosphonate starting materials are:

5 diethyl 2-thienylmethylphosphonate,
diethyl 4-pyridylmethylphosphonate,
diethyl 4-methylbenzylphosphonate,
diethyl benzylphosphonate,
diethyl 4-chlorobenzylphosphonate,
diethyl 3-chlorobenzylphosphonate,
10 diethyl 2-chlorobenzylphosphonate,
diethyl 2-pyridylmethylphosphonate,
diethyl 3-thienylmethylphosphonate,
diethyl 2-furanylmethylphosphonate,
diethyl 2-fluorobenzylphosphonate,
15 diethyl 3-pyridylmethylphosphonate,
diethyl 4-ethoxycarbonylbenzylphosphonate,
diethyl 4-(phenylaminocarbonyl)benzyl
phosphonate,

20 As outlined on Flowsheet XXVI, the Δ^{20} olefins IIIa and IIIc can be reduced with e.g. 10% palladium on carbon in a suitable solvent, e.g. methanol, ethanol, dioxane, acetic acid and the like, at room temperature under 1-50 psig hydrogen atmosphere to form IVa and IVc. Compound IVc can be further reacted to form
25 the Δ' olefin IVb by the procedure of Dolling et al using dichlorodicyanobenzoquinone, see JACS (1988), Vol 110, pp 3318-3319. Alternatively IVb can be formed by reacting IVc with benzeneselenic anhydride in refluxing chlorobenzene. The 4-
30 nitrogen in IIIb and IVb can be alkylated with methyl iodide in the presence of sodium hydride in e.g. dry dimethylformamide solvent to give III d and IV d.

Note that the 4-methyl group in the appropriate compounds in Flowsheet A can be replaced with a 4-ethyl group to

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prepare the corresponding 4-ethyl analogs of IIIa, IVa, IIIc, and IVd.

5 The aldehydes A, B and C can be reacted with diethyl α -methyl-benzylphosphonate (US 4,515,883) in the Wadsworth-Emmons modification of the Wittig reaction and the corresponding products hydrogenated, alkylated on the 4-nitrogen and dehydrogenated as outlined in Flowsheet XXVI to give compounds IIIa-d and IVa-d with R^2 = phenyl and R^3 = methyl.

10 Methyl ketone D (see Flowsheet XXVII, below) and its preparation is described in J. Med. Chem., 1984, Vol. 27, p. 1690-1701, by G. H. Rasmusson et. al (see Compound 4d.) These compounds can be prepared by reacting the S-(2-pyridyl)androstan-3-one-17 β -thio-carboxylate with methylmagnesium chloride under appropriate Grignard conditions.

15 Methyl Ketone E can be prepared by reacting N-methoxy-N-methyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (4) with excess methylmagnesium bromide in tetrahydrofuran.

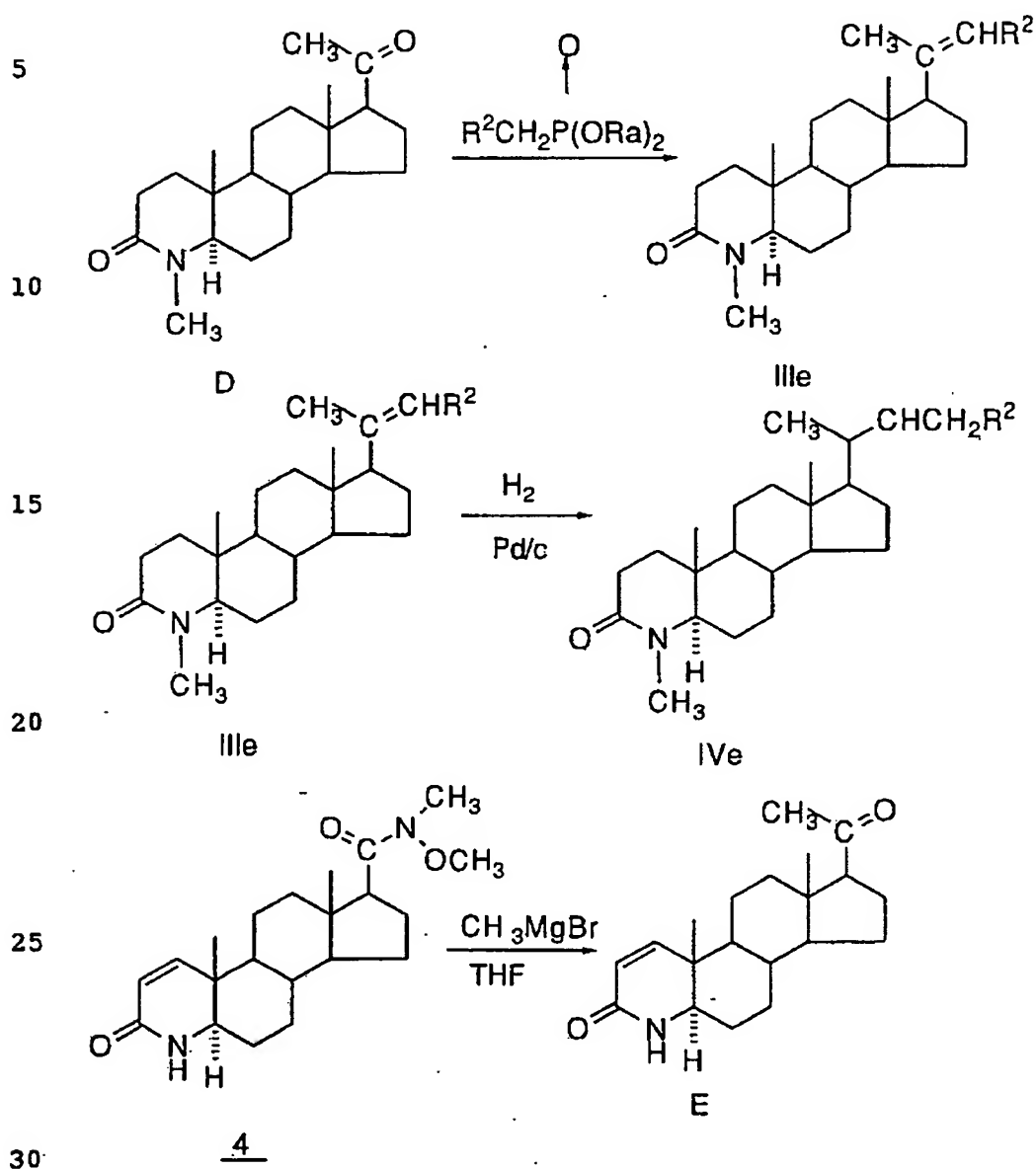
20 The above 17-methylketones D and E can be reacted with the phosphonate ylids described above in an analogous manner to achieve the 20-methyl pregn-20-en-3-one compounds IIIi and IIIj as illustrated in the following Flowchart XXVII.

25

30

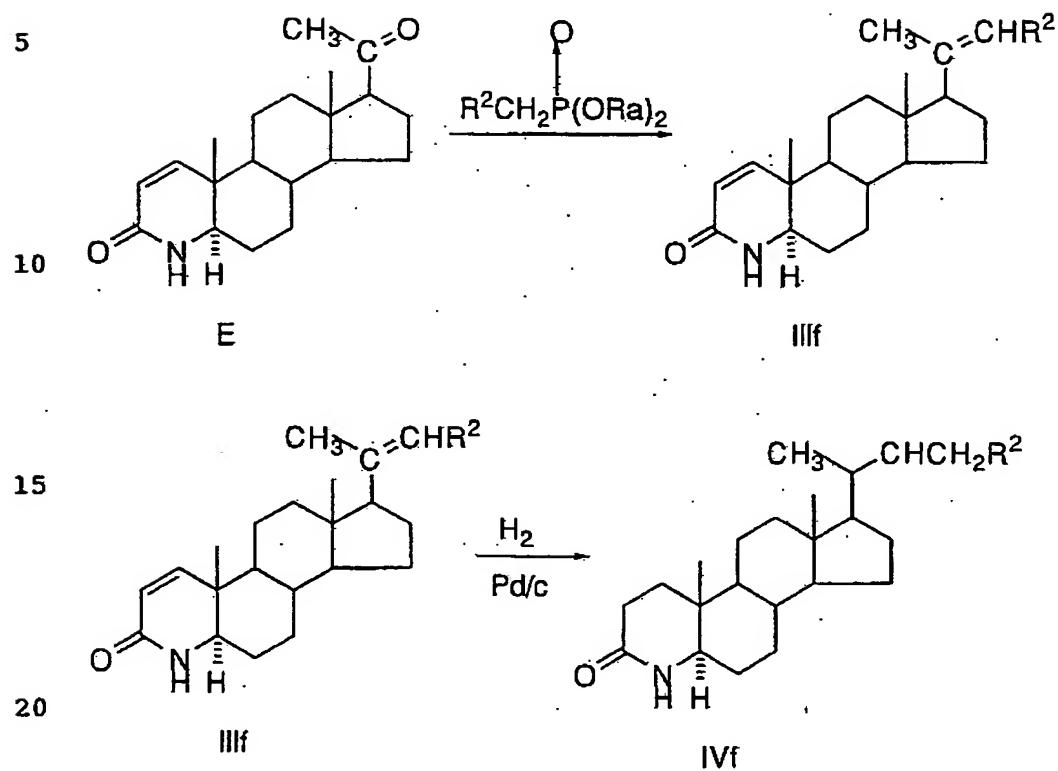
- 201 -

FLOWSHEET XXVII



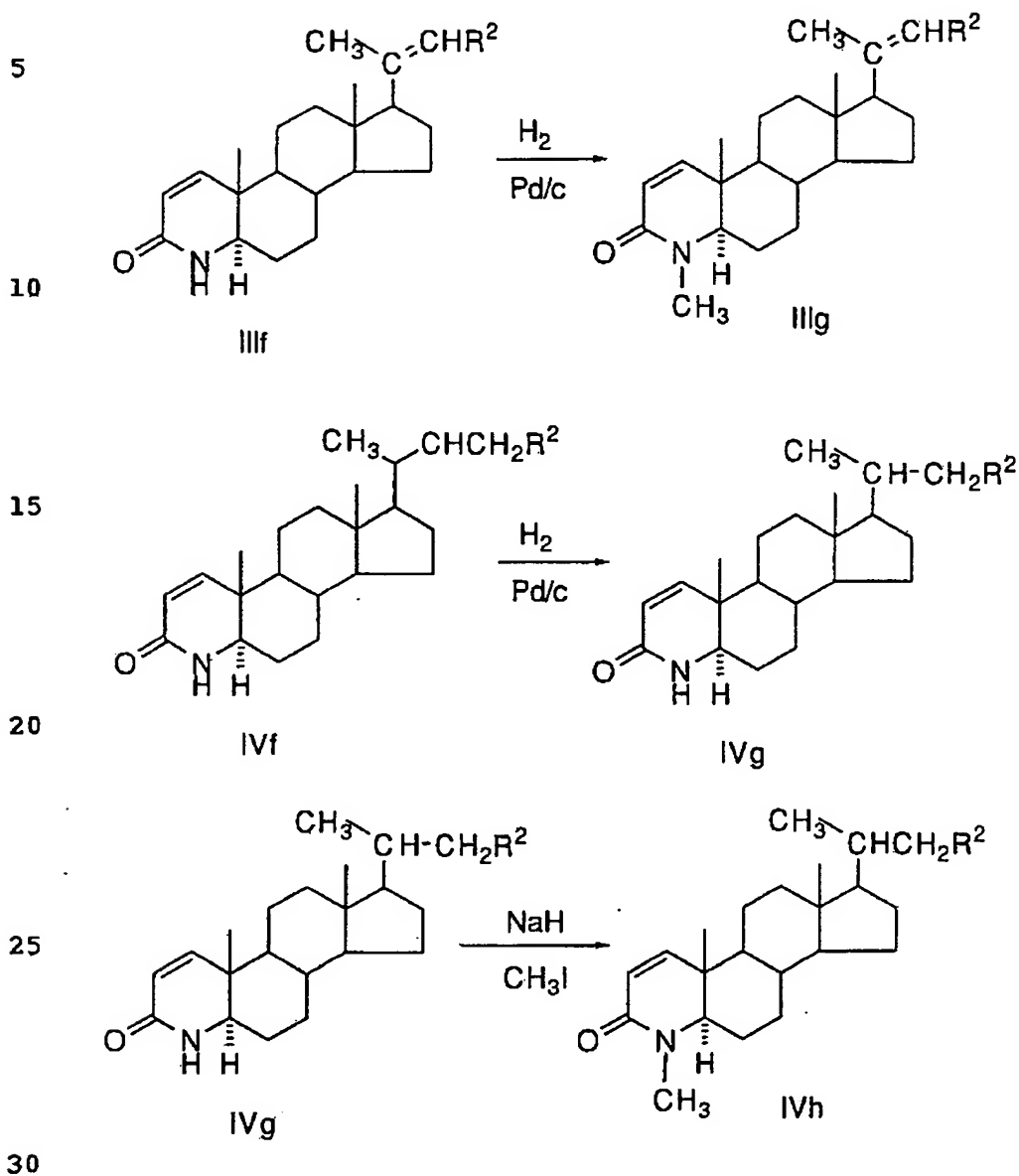
- 202 -

FLOWSHEET XXVII (CONT'D)



- 203 -

FLOWSHEET XXVII (CONT'D)



As outlined in Flowsheet XXVII, IIIe and IIIf can be hydrogenated as above to give IVe and IVf. Compound IVf can be dehydrogenated as described above to the Δ' -compound IVg.

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Compounds IIIf and IVg can be methylated on the 4-nitrogen to give IIIg and IVh.

Also the amide 4 can be reacted with ethylmagnesium bromide to give ethyl ketone versions of D and E. Using the
5 reactions outlined in Flowsheet B compounds IIIe-g and IVe-h with the 20-methyl replaced by a 20-ethyl can be prepared.

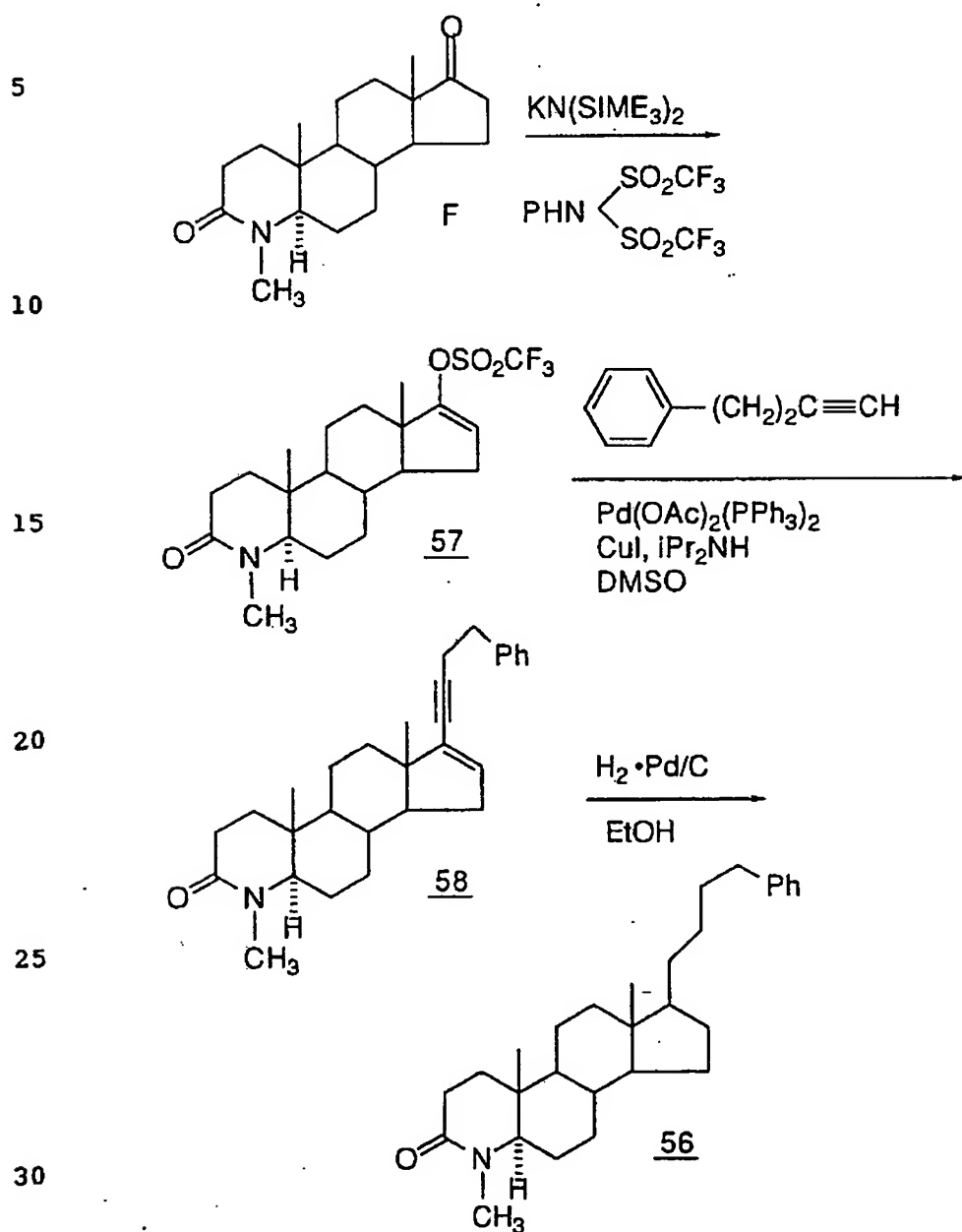
Ketone F (Flowsheet XXVIII) can be prepared by conventional techniques, including oxidation of the corresponding
17- β -ol with e.g. Jones reagent, and is known in the art in J. Med.
10 Chem. 1984, Vol. 27, p. 1690-1701 by G. H. Rasmusson et. al., (see Compound 22 on p. 1693).

Ketones G and H can be prepared by Jones reagent oxidation of the corresponding 17 β -alcohols described in the above
reference. Using the reactions shown in Flowsheet XXVI, the
15 ketones F, G, and H are converted into compounds IIIh-k and IVh-l as seen in Flowsheet C.

As indicated in Example 67, below, the 17 β -3-phenylpropyl compound can be prepared from aldehyde A by a
phosphonate olefination with diethyl benzoylmethylphosphonate
20 followed by reduction of the ketone and double-bond by hydrogenation with palladium on carbon catalyst in ethanol. Using the reaction sequences outlined in Flowsheet XXVI, the 4-H, Δ^4 -H, and 4-CH₃- Δ^4 analogs can be prepared starting from aldehydes A or
25 B.

30

FLWSHEET XXVIII



As shown in Flowsheet XXVIII, the 17 β -3-phenylbutyl compound 56 can be prepared from the ketone F by conversion of

- 206 -

the latter to the Δ^{16} -17-trifluoromethylsulfonate 57 with potassium hexamethyldisilazide and N-phenyltrifluoromethanesulfinimide (Tetrahedron Lett. 24, 979 (1983)). Palladium-catalyzed coupling of 57 with 4-phenyl-1-butyne (Synthesis, 320 (1986)) can give the enyne 58 which can be hydrogenated to the desired 17 β -3-phenyl-butyl compound 56.

10

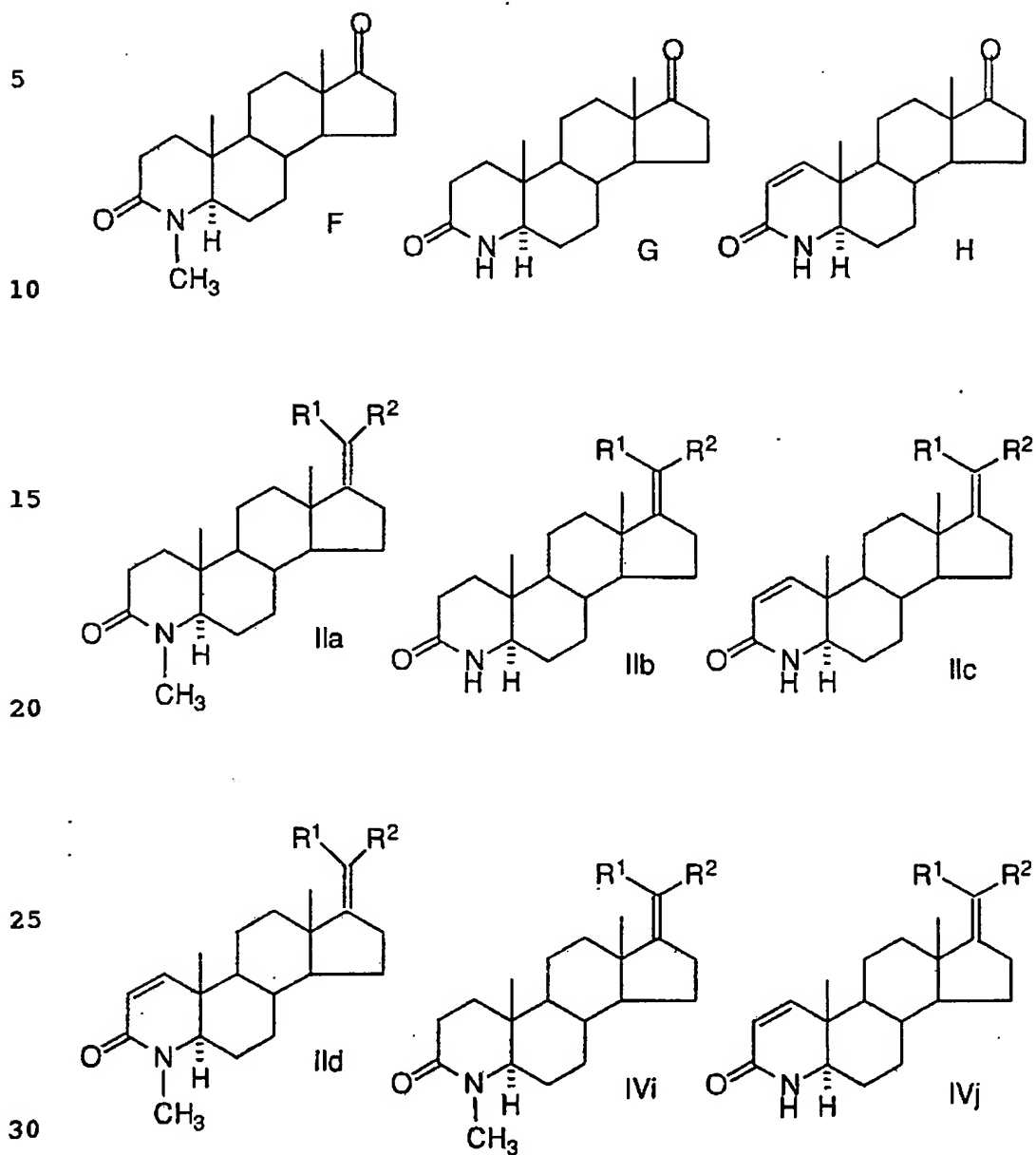
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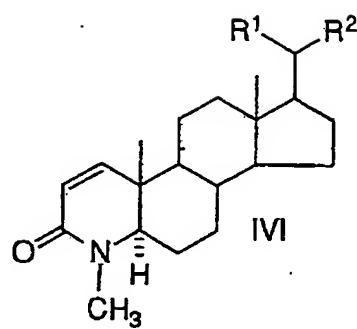
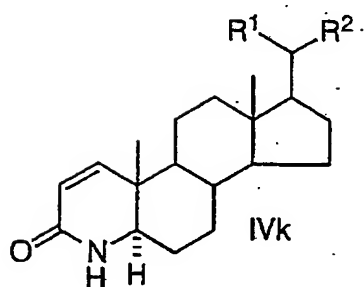
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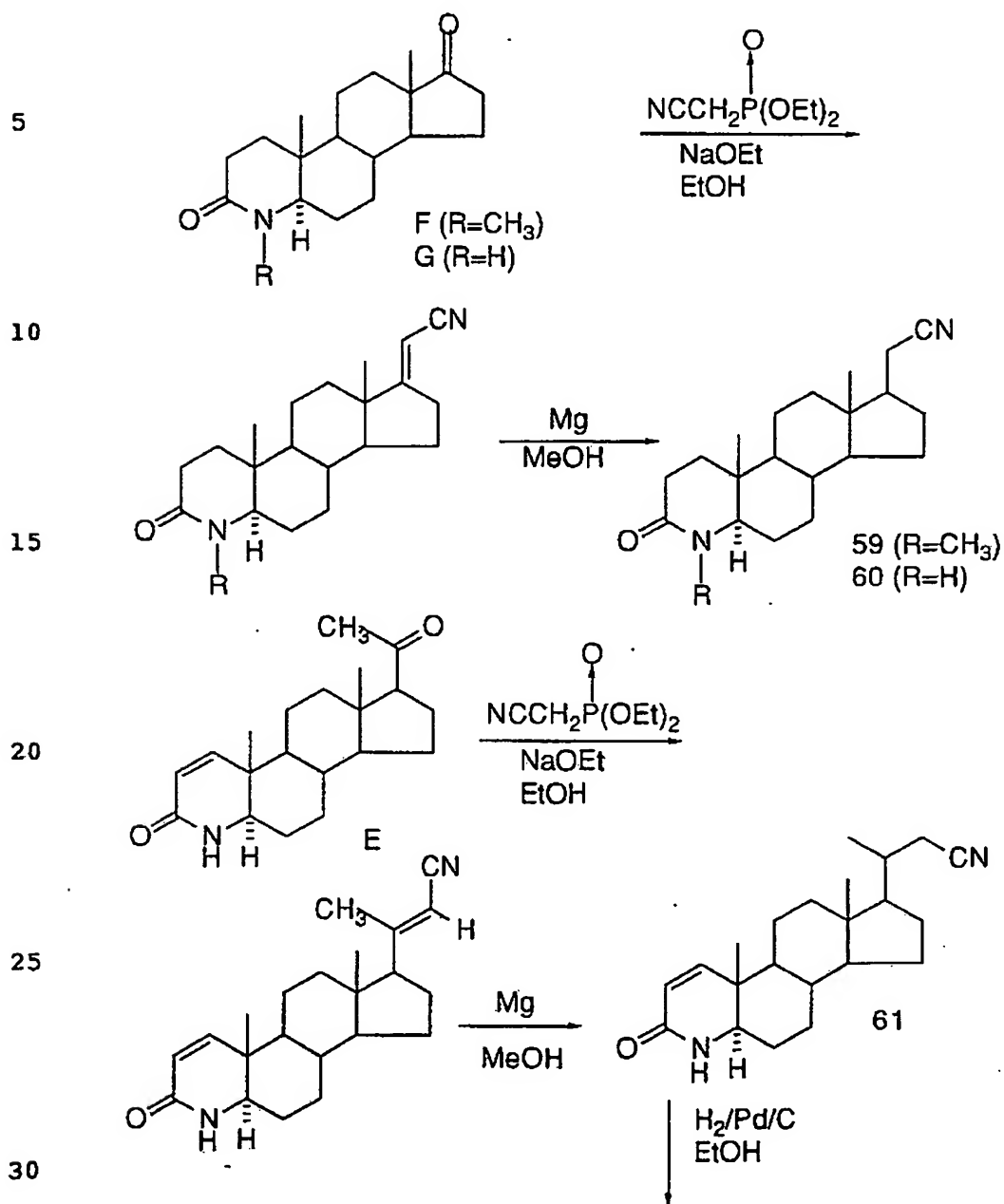
- 207 -

FLWSHEET XXIX

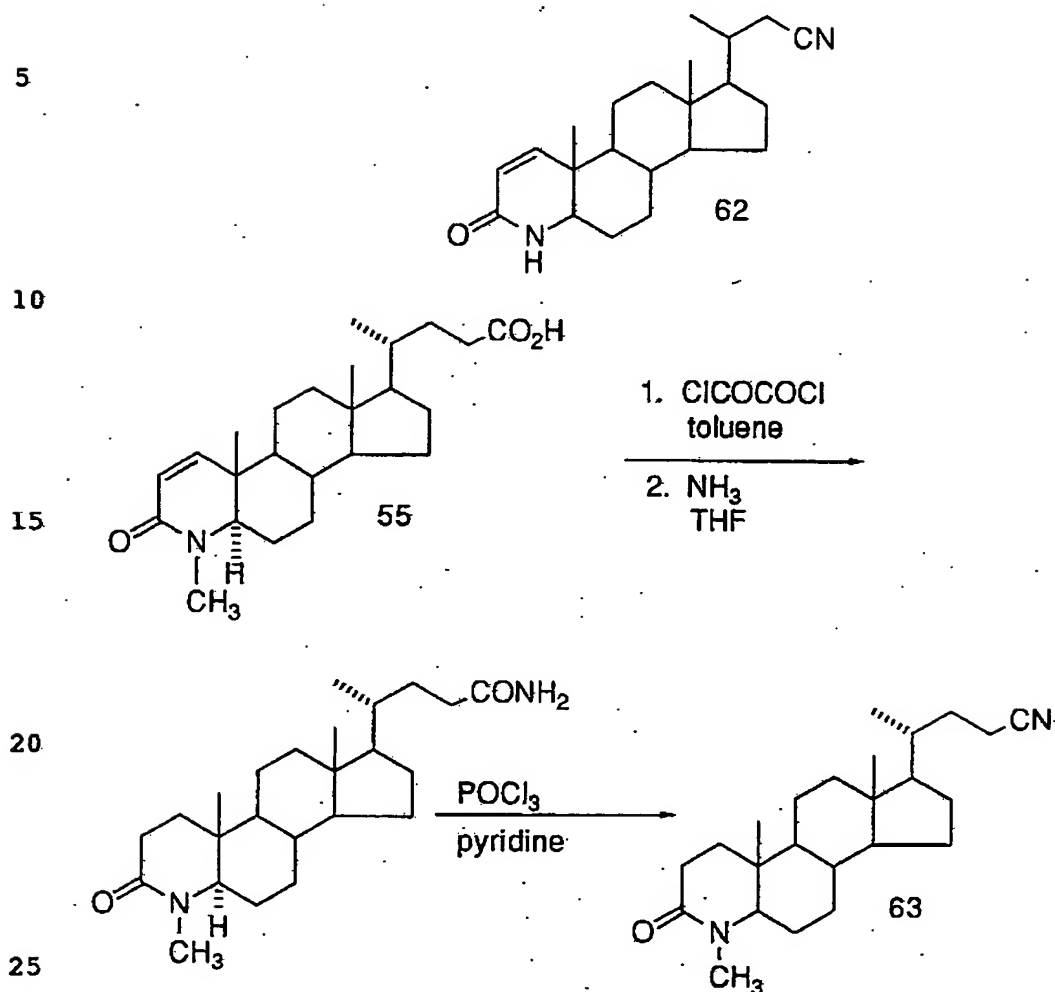
- 208 -

FLWSHEET XXIX (Cont'd)

- 209 -

FLWSHEET XXX

- 210 -

FLWSHEET XXX (Cont'd)

As described in Example 68, the nitriles 54 (R=CH₃, H) were prepared from a "second order" Beckmann rearrangement on the homologous carboxylic acids (55, R=CH₃, H) with sodium nitrite in trifluoroacetic acid and trifluoroacetic anhydride. (J. of Lipid Research 29 1387 (1988)).

The synthesis of other nitriles is outlined in Flowsheet XXX. The pregnane-21-carbonitriles 59 and 60 can be prepared from the ketones F and G by phosphonate olefination with diethyl

- 211 -

cyanomethylphosphonate (Steroids 27, 431 (1976)) followed by reduction with magnesium in methanol (J. Org. Chem. 40, 127 (1975)). By the same reaction sequence the ketone E can be converted into the Δ^1 -4-H-24-nor cholane-23-nitrile 61 and its reduction product 62. The 24-cholane-24-carbonitrile 63 can be prepared from the cholanic acid 55 by conversion to the primary amide with oxalyl chloride and ammonia followed by dehydration with POCl₃ in pyridine (J. Med. Chem. 29, 2298 (1986)). Similarly the 17-butyric (64, n=1) and valeric (n=2) acids, prepared by palladium-catalyzed coupling of 57 with 3-butyric and 4-pentynoic acids followed by hydrogenation, can be converted into the nitriles 66 (n=1,2).

EXAMPLE 67

Synthesis of 4,7 β -Dimethyl-4-aza-Androst-5-en-3-one-17 β -ol, t-butyldimethylsilyl ether, (68)

To a solution of the product of Example 8 (17 β -(t-butyldimethylsilyloxy)-7 β -methyl-5-oxo-A-nor-3,5-secoandrostan-3-oic acid), 840 mg in 5 ml ethylene glycol was added 1.5 g sodium acetate and 737 mg. methylamine hydrochloride. After stirring the reaction mixture 4 hours at 180°C, the mixture was cooled, diluted with water, extracted with ethyl acetate, dried and concentrated to afford crude title compound 68. Proton NMR confirmed the assigned structure.

EXAMPLE 68

Synthesis of 4,7 β -Dimethyl-4-aza-Androst-5-en-3-one-17 β -ol, (69)

To a solution of 700 mg of 68 from Example 67, in 20 ml of acetonitrile at 0°C was added 500 microliters. aqueous HF. After stirring the reaction mixture for one hour, the HF was neutralized with aqueous sodium carbonate, diluted with water, acetonitrile removed under vacuum, and the residue extracted with

- 212 -

ethyl acetate. The organic layer was dried, concentrated to give crude title compound 69 which was further purified by preparative chromatography on silica gel using 3:1 chloroform/acetone.

5

EXAMPLE 69

Synthesis of 4,7 β -dimethyl-4-aza-androstan-3-one-17 β -ol. (70)

To a solution of 69 from Example 68, being 350 mg in 10 ml acetic acid was added 100 mg platinum dioxide and the
10 resulting mixture was evacuated and flushed with hydrogen. The reaction was shaken overnight at room temperature under 40 Psig hydrogen pressure. The solution was filtered concentrated. The residue was worked up with ethyl acetate, the organic layer was then concentrated under vacuum, diluted with ethyl acetate, washed with
15 aqueous NaHCO₃, brine, dried, concentrated to yield the title compound 12. Mass Spec: 320 (M+1).

EXAMPLE 70

20

Synthesis of 17 β -pivaloyloxy-4,7 β -Dimethyl-4-Aza-Androstan-3-one. (71)

To a solution of 70 from Example 69, being 60.2 mg in 4 ml methylene chloride and 200 ml pyridine was added 15 mg DMAP (4-dimethylaminopyridine) followed by 68.66 mg pivaloyl
25 chloride, i.e., trimethyl acetyl chloride. After stirring for 24 hours, the reaction mixture was diluted with ethyl acetate, washed with water, then aqueous sodium carbonate and brine. The organic layer was dried, concentrated to a residue, which was purified by
30 preparative chromatography on silica gel using 3:1 chloroform/acetone as eluant to yield pure title compound 71. Proton NMR confirmed the assigned structure.

EXAMPLE 71

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Synthesis of 17 β -(t-Butylaminocarbonyloxy)-4,7-dimethyl-5 α -4-aza-Androstan-3-one. (72)

To a solution of 70, 51 mg in 4 ml methylene chloride was added DBU (200 microliters) followed by 63.65 mg. t-butylisocyanate. After stirring the mixture for 48 hours at room temperature, the reaction mixture was diluted with ethyl acetate, the organic layer washed with water, brine, dried and concentrated to a residue which was purified by preparative chromatography over silica gel using 3:1 CHCl₃/acetone to yield pure title compound 72.

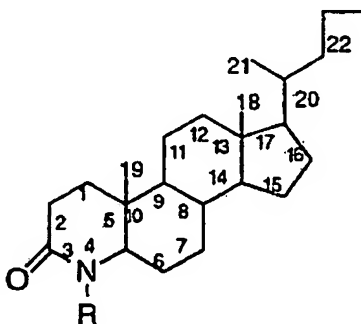
EXAMPLE 72

Synthesis of 17 β -Methoxycarbonyl-4-methyl-4-aza-androst-5-en-3,7-dione

Following the analogous oxidation procedure of Example 3, 17 β -methoxycarbonyl-4-methyl-4-aza-5 α -androst-3-one, known in the art, was analogously treated to yield the title compound.

The following Table 5 lists the unique proton NMR values (400 MHz in CDCl₃) for several of the above-described compounds. The data are reported as: s = singlet, d = doublet, m = multiplet, J = coupling constant. The absorption values are given del (d) units and are illustrated for the C-18, C-19 and methyl protons and protons associated with unique portions of the molecule.

The numbering of the steroid is given by the following structure;



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NMR DATA

	<u>Compound No</u>	<u>C-18 CH₃</u>	<u>C-19 CH₃</u>	<u>Others</u>
5	68	0.72	1.02	7 Me, 3H, d, 1.04 J=6.5 6H, 1H, d, 4.78 J=3
10	69	0.78	1.02	7 Me, 3H, d, 1.06, J=6.5 6H, 1H, d, 4.79, J=3
15	70	0.74	0.86	7 Me, 3H, d, 1.02, J=6.5 5H, 1H, dd, 3.10 J=4.5 J=13.5
20	71	0.82	0.85	N-CH ₃ , 3H, S, 2.90 C-5, 1H, dd, 3.01 J=12.6 J= 3.7
25				C-7B-CH ₃ , 3H, d, 1.02, J= 6.5

NMR DATA (CONTD)

30	<u>Compound No</u>	<u>C-18 CH₃</u>	<u>C-19 CH₃</u>	<u>Others</u>
	72	0.76	0.82	N-CH ₃ , 3H, S, 2.89 C-5, 1H, dd, 3.01 J= 3.7 J=12.6

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C-7 β -CH₃, 3H; d,
1.02, J= 6.5

5 Also included in the invention are the following
compounds:

4, 7 β -dimethyl-4-aza-5 α -androstan-3, 17-dione,
10 17-oximino-4, 7 β -dimethyl-4-aza-5 α -androstan-3-one.

The compounds can be by analogous procedures
described in J. Med. Chem. 29, 2998-2315 (1986) by Rasmusson et
al. for preparing the 17-one. The 17-one can then be reacted with
15 ammonia, substituted amines, hydrazine, substituted hydrazine, by
known analogous procedures to produce the above described
compounds.

Also included with the scope of this invention are 4-N-X
analogues where X is OH, NH₂ or SCH₃. The 4-N-OH and 4-N-NH₂
20 derivatives can be made with incorporating hydroxylamine or
hydrazine, respectively, in place of methylamine in the seco acid ring
A closure for the starting androstanes as described in J. Med. Chem.
29, 2998-2315 (1986) by Rasmusson et al. Further, reaction of the
anion of the saturated 4-N-H androstanes, wherein the anion is
25 generated from the N-NH precursor by sodium hydride, and
methylsulphenyl chloride can produce the corresponding 4-N-S-CH₃
derivatives. Thus, substituent on the 4-N position also includes OH,
NH₂ and S-CH₃.

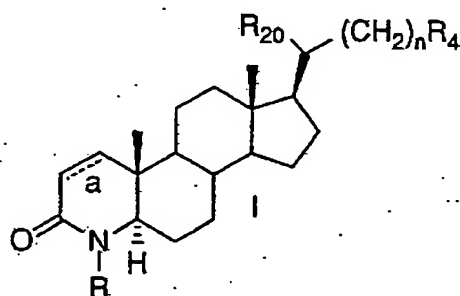
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The present invention also discloses novel 17 β -ester, amide, and ketone derivatives of 4-aza-5 α -androstan-3-one compounds of the general structural formula XXII:

5

10



wherein:

15

dashed line a can represent a double bond when present;

R is selected from hydrogen, methyl, ethyl, hydroxyl, amino, and methylthio;

20

R₂₀ is selected from hydrogen or methyl;

n is an integer from 0 to 10;

R₄ is selected from:

25

(a) COR₁, where R₁ is C₆-C₁₀ aryl, substituted C₆-C₁₀ aryl, and heteroaryl;

30

(b) CONHR₂, where R₂ is substituted phenyl, heteroaryl, substituted heteroaryl, or C₇ to C₁₂ cycloalkyl;

(c) CO₂R₃, where R₃ is C₆-C₁₀ aryl, substituted C₆-C₁₀ aryl, or C₇-C₁₂ cycloalkyl;

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where the above aryl and heteraryl radicals can also be fused with a benzo or another heteroaryl ring and can further be substituted with one or more substituents; and pharmaceutically acceptable salts and esters thereof.

5 Dashed line "a" can independently be a double bond and when present, the compound is a delta-1-ene.

R₁ and R₃ can be a C₆-C₁₀ aryl including phenyl, benzyl, 1- and 2-phenethyl and naphthyl.

R₂ can be a phenyl group.

10 R₁ and R₂ can also be 5-6 membered heteroaryl radicals being fully unsaturated containing 1-4 nitrogen atoms, e.g. pyridyl, pyrrol, imidazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, pyrazolyl, or triazolyl; containing 1-2 oxygen or sulfur atoms, e.g. thienyl, furanyl; or in combination with 1-2 nitrogen atoms, e.g. isothiazolyl, thiazolyl, isoxazolyl, oxazolyl or thiadiazolyl; or fused with a benzo
15 ring, e.g. quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, indolyl, carbazolyl; or fused with another heteroaryl ring, e.g. purinyl, and the like.

20 The C₇ - C₁₂ cycloalkyl in R₂ and R₃ can be 1-, 2-adamantyl, norbornyl, and bicyclo[2.2.2.]octyl.

The aryl or heteroaryl ring in R₁ and R₃ as well as the phenyl group in R₂ can be unsubstituted or substituted with one or more of the following substituents providing the substitution leads to a chemically inert, but biologically active 5 α reductase inhibitor:

25 The ring substituents include:

C₁-C₈ straight or branched alkyl; e.g. methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, n-hexyl, iso-hexyl, n-butyl, n-octyl, iso-octyl, t-octyl, and the like; C₂-C₈
30 straight or branched alkenyl, e.g. ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 1-hexenyl, 1-heptenyl, 1-octenyl, 2-octenyl, and the like;

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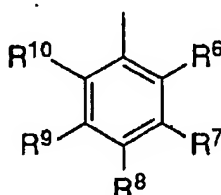
- C₃-C₈ cycloalkyl e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methyl-cyclobutyl, cyclopentyl, cyclohexyl, 1-methyl-cyclohexyl, 2-methylcyclohexyl, 2-ethylcyclohexyl, and the like;
- 5 C₂-C₈ alkynyl e.g., 1-ethynyl; 1-propynyl, 2-propynyl, 2-butynyl, 2-pentynyl, 1-hexynyl, 1-heptynyl, 1-octynyl;
- 10 CONR⁴R⁵ where R⁴ and R⁵ independently are H, C₁-C₈ alkyl, as defined above, C₃-C₈ cycloalkyl as defined above, C₁-C₄ perhaloalkyl e.g., trifluoromethyl, perfluoromethyl, trichloromethyl, preferably perfluoroalkyl; phenyl, or substituted phenyl, as described below;
- 15 COR⁴, where R⁴ is defined above, including acetyl, isobutylcarbonyl, benzoyl and the like;
- S(O)_n R⁴, where n is 0-2 and R⁴ is defined above, including methylsulfinyl, methylsulfonyl, phenylsulfonyl, 4-chlorophenylsulfinyl and the like;
- 20 OCOR⁴, where R⁴ is defined above, including acetoxy, propionyloxy, benzoyloxy, 4-chlorobenzoyloxy and the like.
- SO₂NR⁴R⁵ where R⁴ and R⁵ are described above, including sulfonamido, N-methylsulfonamido, N-phenylsulfonamido, N,N-dimethylsulfonamido and the like;
- 25 NR⁴(CO)R⁵, wherein R⁴ and R⁵ are defined above, including; acetylamino, benzoylamino, N-methylbenzoylamino and the like;
- NR⁴(CO)NHR⁵, wherein R⁴ and R⁵ are described above, including; ureido, N-methylureido, N-methyl-N¹-phenylureido and the like;
- 30 NHSO₂R⁴, R⁴ being defined above, including methylsulfonylamino, phenylsulfonylamino and the like;
- OR⁴, where R⁴ is defined above, including methoxy, phenoxy, 4-chlorophenoxy and the like.

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NR⁴R⁵, wherein R⁴ and R⁵ are described above,
including amino, methylamino, dimethylamino, anilino and the like;
Cyano, nitro, halo, including: fluoro, chloro, bromo and
iodo;

Perhalo C₁-C₄ alkyl, including: trifluoromethyl,
perfluoroethyl, trichloromethyl and the like.

CO₂R⁴, wherein R⁴ is defined above, including
CO₂CH₃, CO₂Ph, CO₂-(1-adamantyl) and the like; phenyl and
substituted phenyl of the formula:



wherein the radicals R⁶-R¹⁰ each can represent one or more of the
substituents defined above, including; hydrogen, 4-chlorophenyl, 4-
fluorophenyl, 4-methoxyphenyl, 4-phenoxy and the like.

Unless otherwise indicated the 17-substituents herein
described are assumed to be in the β configuration

Representatives of this group of compounds of the
present invention include the following:

21-benzoyl-4-aza-5 α -pregnan-3-one,
21-benzoyl-4-methyl-4-aza-5 α -pregnan-3-one,
21-(2-methoxybenzoyl)-4-aza-5 α -pregn-1-ene-3-one,
4-methyl-21-(2-trifluoromethylbenzoyl)-4-aza-5 α -pregn-1-en-
3-one,
20-benzoyl-4-methyl-4-aza-5 α -pregnan-3-one,
23-(2-fluorobenzoyl)-4-methyl-24-nor-4-aza-5 α -cholane-3,23-
dione,
23-(3-pyridyl)-24-nor-4-aza-5 α -chol-1-ene-3,23-dione,
4-methyl-24-(2-pyridyl)-21-nor-4-aza-5 α -cholane-3,24-dione,

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- 17 β -[5-(3-chlorobenzoyl)pentyl]-4-aza-5 α -androstan-3-one,
17 β -(6-benzoylhexyl)-4-methyl-4-aza-5 α -androstan-3-one,
17 β -(10-benzoyldecyl)-4-aza-5 α -androst-1-en-3-one,
4-methyl-21-(2-thienyl)-4-aza-5 α -pregnane-3,21-dione,
5 24-(2-pyrazinyl)-4-aza-5 α -chol-1-ene-3,24-dione,
4-ethyl-(2,6-dimethoxybenzoyl)-4-aza-5 α -pregnan-3-one,
N-(4-acetylphenyl)-4-methyl-3-oxo-4-aza-5 α -pregnane-21-
carboxamide,
N-(4-acetylphenyl)-3-oxo-4-aza-5 α -pregnane-21-carboxamide,
10 4-methyl-3-oxo-N-(4-pyridyl)-4-aza-5 α -pregnane-21-
carboxamide,
3-oxo-N-(4-pyridyl)-4-aza-5 α -pregnane-21-carboxamide,
N-(2-adamantyl)-3-oxo-4-aza-5 α -pregnane-21-carboxamide,
N-(2-adamantyl)-4-methyl-3-oxo-4-aza-5 α -pregnane-21-
15 carboxamide,
3-oxo-N-(4-pyridyl)-4-aza-5 α -pregnan-21-amide,
4-methyl-3-oxo-4-(4-pyridyl)-4-aza-21-nor-5 α -cholan-24-
amide,
4-methyl-3-oxo-N-(3-pyridyl)-4-aza-5 α -pregnane-21-
20 carboxamide,
4-methyl-3-oxo-N-(2-pyridyl)-4-aza-5 α -pregnane-21-
carboxamide;
N-(1-adamantyl)-4-methyl-3-oxo-4-aza-5 α -pregnane-20(S)-
carboxamide,
25 N-(4-acetylphenyl)-4-methyl-3-oxo-4-aza-5 α -pregnane-20(S)-
carboxamide,
N-(4-chlorophenyl)-4-methyl-3-oxo-4-aza-5 α -cholan-24-
amide,
N-(4-acetylphenyl)-4-methyl-3-oxo-4-aza-5 α -cholan-24-
30 amide,
3-oxo-N-(4-trifluoromethylphenyl)-4-aza-5 α -cholan-24-
amide,
4-methyl-3-oxo-N-(4-pyridyl)-24-nor-4-aza-5 α -cholan-24-
amide,

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- N-(1-adamantyl)-11-(4-methyl-3-oxo-4-aza-5 α -androstan-17 β -yl)undecanamide,
N-(2-pyridyl)-6-(4-methyl-3-oxo-4-aza-5 α -androstan-17 β -yl)hexanamide,
5 N-(3-pyridyl)-5-(3-oxo-4-aza-5 α -androst-1-en-17 β -yl)pentanamide,
N-(2-thienyl)-7-(4-methyl-3-oxo-4-aza-5 α -androstan-17 β -yl)heptanamide,
3-oxo-N-(2-pyrazinyl)-4-aza-5 α -pregnan-21-amide, 4-methyl-
10 3-oxo-N-(2-t-butylphenyl)-4-aza-5 α -cholane-24-carboxamide,
4-methyl-3-oxo-N-(2-cyanophenyl)-4-aza-chol-1-ene-24-carboxamide,
N-(2-bicyclo[2.2.2]octyl)-9-(3-oxo-4-aza-5 α -androstan-17 β -yl)nonanamide,
15 1-adamantyl 4-methyl-3-oxo-4-aza-5 α -pregnane-20(S)-carboxylate,
phenyl 4-methyl-3-oxo-4-oxo-4-aza-5 α -pregnane-20(S)-carboxylate,
20 2-(t-butyl)phenyl 4-methyl-3-oxo-4-aza-5 α -pregnane-21-carboxylate,
2-methoxyphenyl 4-methyl-3-oxo-4-aza-5 α -pregnane-21-carboxylate,
phenyl 3-oxo-4-aza-5 α -pregnane-21-carboxylate,
25 phenyl 4-methyl-3-oxo-4-aza-5 α -pregnane-21-carboxylate,
phenyl 5-(4-methyl-3-oxo-4-aza-5 α -androstan-17 β -yl)pentanoate,
2-(t-butyl)phenyl 3-oxo-4-aza-5 α -pregnan-21-oate,
2,6-dimethoxyphenyl 3-oxo-4-aza-5 α -pregn-1-en-21-oate,
30 2-adamantyl 8-(4-methyl-3-oxo-4-aza-5 α -androstan-17 β -yl)octanoate,
2,6-dimethylphenyl 3-oxo-4-aza-5 α -pregn-1-en-21-oate,
2,6-dichlorophenyl 4-methyl-3-oxo-4-aza-5 α -pregn-1-en-21-ate,

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phenyl 10-(4-methyl-3-oxo-4-aza-5 α -androstan-17 β -
 yl)decanoate,
 N,4-dimethyl-3-oxo-N-(4-pyridyl)-4-aza-5 α -pregnan-21-amide,
 N-methyl-3-oxo-N-(4-pyridyl)-4-aza-5 α -pregnan-21-amide,
 5 4-methyl-3-oxo-N-(4-pyridyl)-4-aza-5 α -pregnane-20-
 carboxamide,
 4-methyl-3-oxo-N-(3-pyridyl)-4-aza-5 α -pregnane-20-
 carboxamide,
 4-methyl-3-oxo-N-(2-pyridyl)-4-aza-5 α -pregnane-20-
 10 carboxamide,
 4-methyl-3-oxo-N-(4-pyridyl)-4-aza-5 α -cholan-24-amide,
 4-methyl-3-oxo-N-(3-pyridyl)-4-aza-5 α -cholan-24-amide,
 4-methyl-3-oxo-N-(2-pyridyl)-4-aza-5 α -cholan-24-amide,
 3-oxo-N-(4-pyridyl)-4-aza-5 α -pregn-1-ene-20-carboxamide,
 15 3-oxo-N-phenyl-4-aza-5 α -pregn-1-ene-21-carboxamide,
 N-(4-methoxyphenyl)-3-oxo-4-aza-5 α -pregn-1-ene-21-
 carboxamide,
 N-(2-imidazolyl)-3-oxo-4-aza-5 α -pregn-1-ene-21-carboxamide,
 3-oxo-N-(4-pyridyl)-4-aza-5 α -pregn-1-ene-21-carboxamide,
 20 3-oxo-N-(3-pyridyl)-4-aza-5 α -pregn-1-ene-21-carboxamide,
 3-oxo-N-(2-pyridyl)-4-aza-5 α -pregn-1-ene-21-carboxamide,
 3-oxo-N-(1,2,4-triazin-3-yl)-4-aza-5 α -pregn-1-ene-21-
 carboxamide,
 3-oxo-N-(3-quinolinyl)-4-aza-5 α -pregn-1-ene-21-carboxamide,
 25 3-oxo-N-(4-pyridyl)-4-aza-5 α -chol-1-en-24-amide,
 3-oxo-N-(3-pyridyl)-4-aza-5 α -chol-1-en-24-amide,
 3-oxo-N-(2-pyridyl)-4-aza-5 α -chol-1-en-24-amide,
 and also including the corresponding compounds wherein the 4-
 hydrogen substituent is replaced by a methyl or an ethyl radical,
 30 and/or a delta-one double bond is present.

The starting materials for these preparations are the
 appropriate carboxylic acids 1, 2, 9, 16, 17, 34, 37, 40, 45, 63,
 64, 68 and 78 (these numbers are with reference to examples 73
 through 84). The source of these carboxylic acids is as follows:

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The synthesis of acid **1** is published in J. Med. Chem.
1984, Vol. 27, p 1690.

Acid **2** was prepared by the same procedure as acid **1**.

The preparation of acid **9** is published in J. Med. Chem.
5 **1984** Vol. 27, p.1690.

The syntheses of acids **16** and **17** are detailed in Example
73, below. The aldehyde **50** was reacted with the methyl
(diethylphosphono)acetate anion to give the olefinic Horner-Wadsworth
reaction product **51**. Hydrogenation to the saturated ester **52** and
10 saponification with aqueous KOH in methanol gave **17**. The same
sequence of reactions starting with the corresponding 4-methyl aldehyde
(J.Med.Chem.1986 Vol. 29, p. 2304, compound 10bg) produced the
acid **16**.

Acid **34** was prepared as outlined in Example 82, below.
15 The nitrile **58** was transformed into the methyl ester **59** by conversion
to the iminoester with anhydrous HCl in methanol followed by
treatment with water. KOH saponification produced the acid **34**.

The acid **37** was synthesized by the Arndt-Eistert
homologation of **16**. Activation of **16** as the mixed anhydride with
20 isobutyl chloroformate and N-methyl morpholine and reaction with
diazomethane gave the diazoketone **53**. Silver benzoate catalyzed
decomposition of **53** in methanol gave the homologous methyl ester **54**.
Saponification have the corresponding acid **37**.

The synthesis of the acids **41** and **65** is published in J.
25 Med. Chem. **1986** Vol. 29, p. 2300. The acids **45**, **63**, and **64** were
prepared by the reaction sequence detailed in Example 83, below.
Palladium catalyzed coupling of the Δ^{16-17} -triflate **60** with methyl 4-
pentynoate using the procedures published in Synlett. **1991** p. 409;
J.Org.Chem. **1992** Vol. 57, p. 973. gave the enyne **61**. Hydrogenation
30 catalyzed with palladium on carbon formed the saturated ester **62** and
KOH saponification gave **45**. Similar reaction sequences using methyl
5-hexynoate and 10-undecynoic acid gave the acids **63** and **64**.

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Starting with the above acids, the novel ketones, amides, and esters listed in Table 5 were prepared using the procedures discussed below and detailed in the Examples.

5 The synthesis of the ketones 32 and 33 are given in Examples 5 and 6. Using the procedures published in J.Med.Chem. 1986 Vol. 29, p. 2310, the acids 16 and 17 were converted into the 2-thiopyridyl esters 55 and 56 by reaction with triphenylphosphine and 2,2'-dithiodipyridine.(Example 77). Low temperature reaction of these 2-thiopyridyl esters with phenyl-magnesium chloride produced the
10 phenyl ketones 32 and 33 (Example 78).

The amides listed in Table 5 were prepared by a variety of procedures:

For the unhindered acids 16, 17, 34, 37, 41, 62, 63, 64, 68 and 78, 4-dimethylaminopyridine (DMAP) catalyzed
15 carbodiimide mediated condensation with the appropriate amine or aniline was used. Either dicyclohexylcarbodiimide (Example 3) or the water soluble 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Example 80) could be used.

For the more hindered acids 1 and 2, formation of the
20 mixed anhydride with isobutyl chloroformate and N-methylmorpholine followed by reaction with the appropriate amine (Example 76) proved to be the best procedure.

For the most hindered acid (9), it was necessary to
25 activate the acid for reaction with an amine by either forming the acid chloride with oxalyl chloride (Example 81) or converting it into the 2-thiopyridyl ester (Example 77).

With hindered or unreactive amines such as 1-adamantamine or 4-acetylaniline, reaction of the 2-thiopyridyl ester alone (Example 77) or with silver trifluoromethylsulfonate catalysis
30 (Example 79) was used to form the amide derivatives.

The ester derivatives in Table 5 were formed from the appropriate acid and alcohol or phenol using the same procedures (Examples 75, 79, and 80) used for the formation of the corresponding amide derivatives

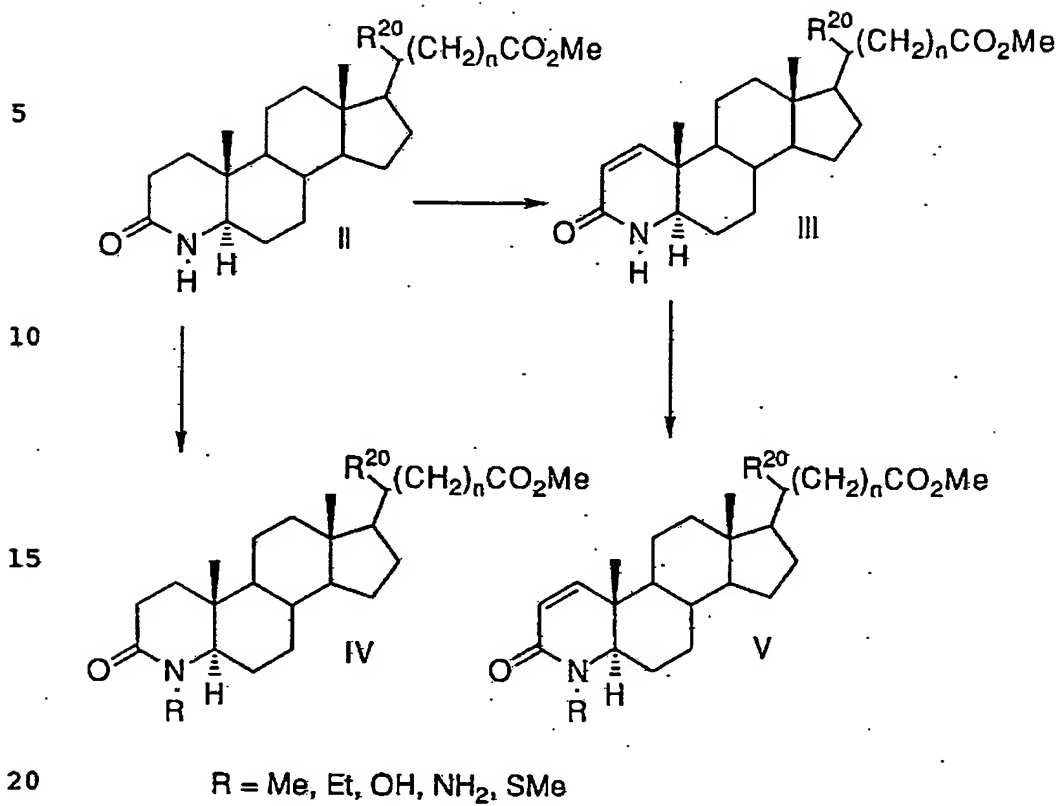
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As outlined in Flowsheet XXXII and detailed in Example 84, the 4-H esters II can be converted into the corresponding Δ^1 -4-H esters (III) by the procedure of Dolling, et al using dichlorodicyanobenzoquinone (J. Amer. Chem. Soc. 1988, Vol. 110, p. 3318-3319) Using this procedure the 4-H esters 52 and 59a were converted into the Δ^1 -4-H esters 69 and 79. The latter esters could be saponified with lithium hydroxide in aqueous t-butanol to the acids 68 and 78. The same conversion of II into III can also be carried out using benzeneselenic anhydride (J. Med. Chem. 1986 Vol. 29, p.2298-2315). Furthermore II and III can be alkylated on the 4-N with methyl or ethyl iodide using sodium hydride in DMF or DMSO to give the 4-methyl- or 4-ethyl-4H esters (IV) or the 4-methyl- or 4-ethyl- Δ^1 esters (V). Also II and III can be converted to the 4-SMe esters IV and V by reaction with sodium hydride and methane-sulfonyl chloride (MeSCl). II and III can also be aminated with hydroxylamine-O-sulfonic acid and oxidized with Oxone-acetone reagent to give the 4-NH₂ and 4-OH esters IV and V, respectively. After saponification of the esters (II-V), the starting acids containing a 4-hydrogen, methyl, ethyl, hydroxy, amino, or methylthio substituent and either with or without a Δ^1 can be prepared, Using the procedures in Examples 73 through 83, these acids can be converted into the corresponding ketone, amide, and ester derivatives.

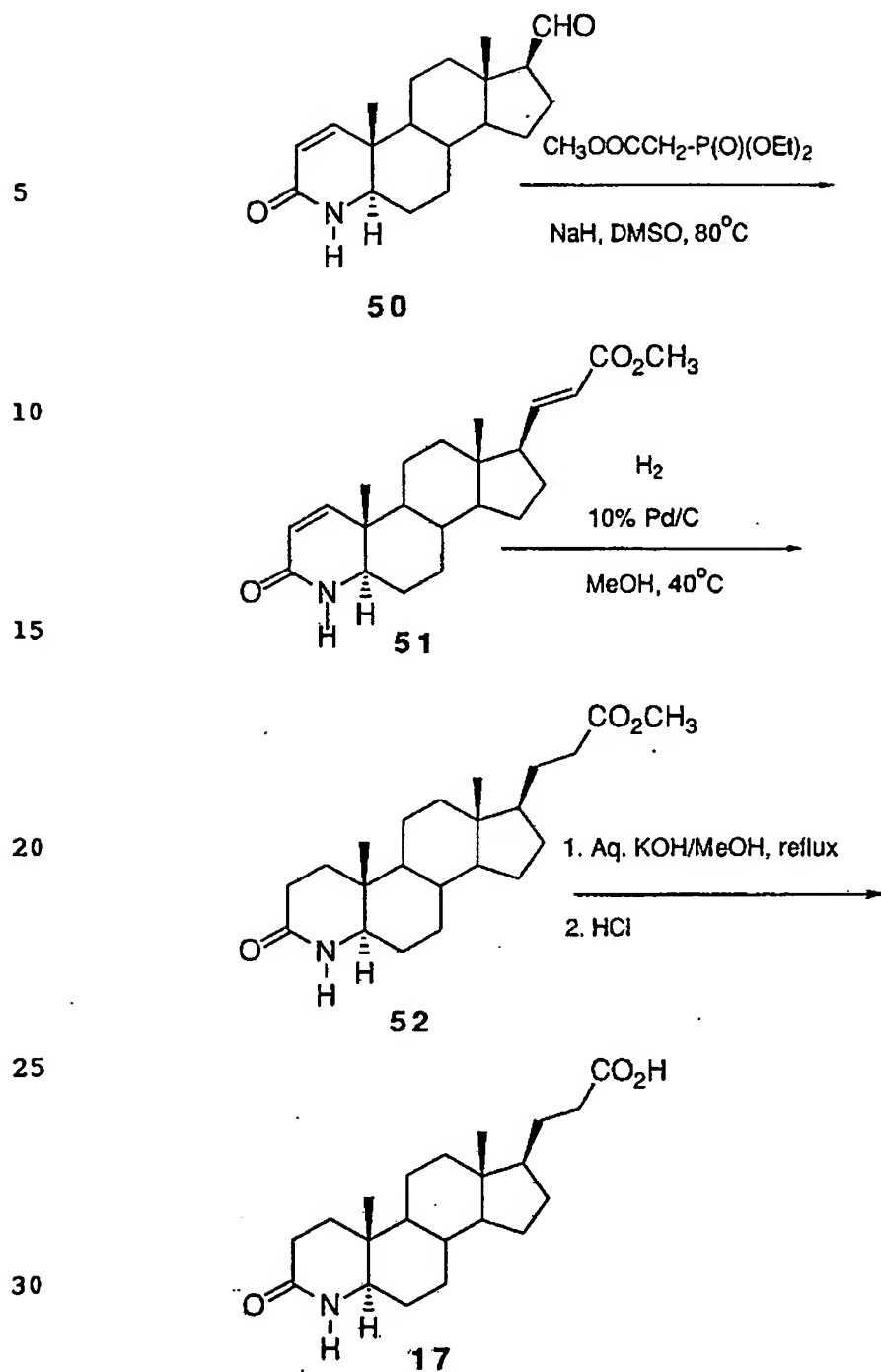
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FLOWSHEET XXXIIEXAMPLE 733-Oxo-4-aza-5α-pregnan-21-carboxylic acid (17)

- 227 -



To a suspension of the aldehyde, (1.0 g, 3.32 mmole) in 12 ml DMSO was added 14.6 mg (3.65 mmole) sodium hydride

- 228 -

(60% in mineral oil) and 698 μ l (3.65 mmole) methyl diethylphosphonoacetate. The mixture was heated under N₂ atmosphere at 80°C for 1 hr. The clear solution was cooled and partitioned between dilute HCl and methylene chloride. The organic phase was washed with water, brine, dried over magnesium sulfate and concentrated *in vacuo* to give 1.2 g crude product. Purification by flash chromatography on silica gel in 4:1 methylene chloride:acetone gave 956 mg of the unsaturated ester [51, NMR, δ =0.66 (s, 3H, 18-Me), 0.97 (s, 3H, 19-Me), 3.72 (s, 3H, OMe), 5.7(d, 1H, Δ^1), 5.82(s, 1H, Δ^{20}), 5.96(bs, 1H, NH), 6.79(d, 1H, Δ^1), 6.92 (dd, 1H, Δ^{20})].

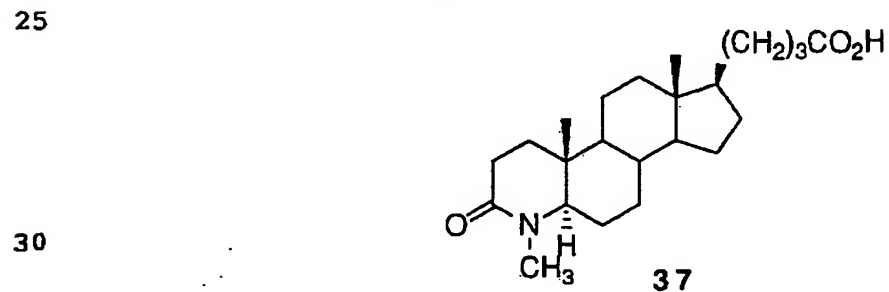
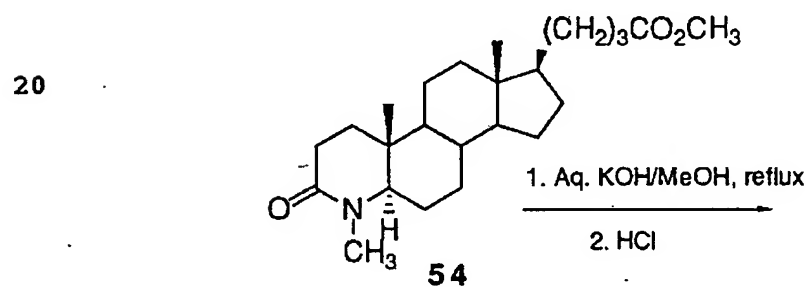
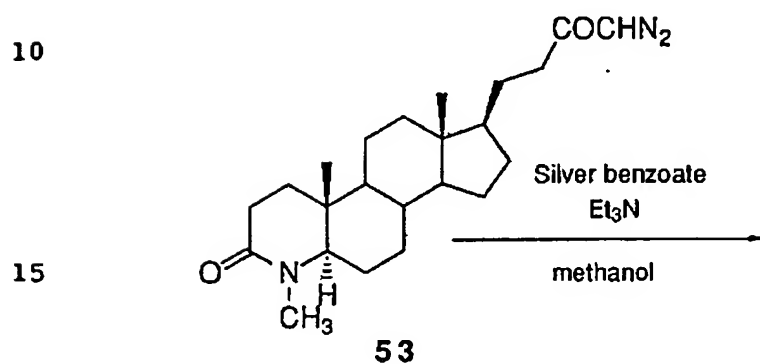
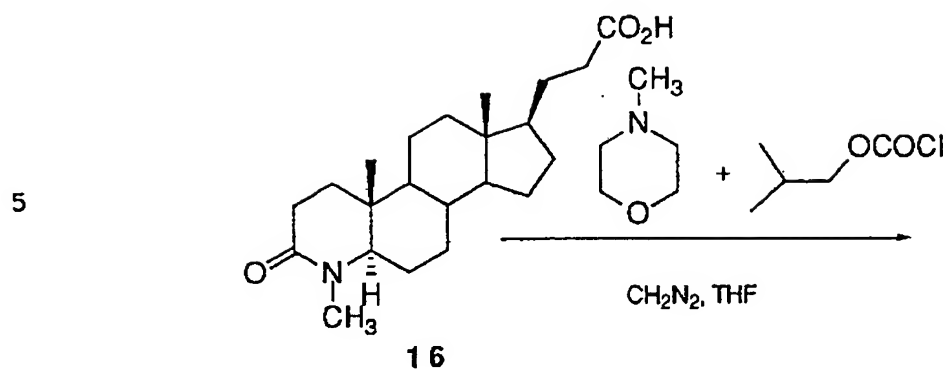
The unsaturated ester (51) (956 mg, 2.67 mmole) was dissolved in 80 ml warm methanol and hydrogenated with 300 mg 10% Pd/C at 40psi at a temperature of 40°C for 3 hrs. The mixture was filtered through a pad of Celite, washing with warm methanol. The filtrate was concentrated *in vacuo* to give 938 mg of the saturated ester (52).

The saturated ester (52) (938 mg, 2.59 mmole) was dissolved in 9 ml methanol containing 863 μ l 9M KOH and refluxed for 1 hr. The mixture was concentrated to a small volume and 100 ml water added. The mixture was cooled to 10°C and brought to pH 1 with concentrated HCl. The resulting precipitate was filtered, washed with water, sucked dry and dried in a vacuum oven at 60°C, 25 in. for 18 hrs, giving 830 mg of the acid (17).

EXAMPLE 74

3-Oxo-4-methyl-4-aza-5 α -21-norcholanic acid (37)

- 229 -



To a solution of the acid (16), (763 mg, 2.66 mmole) and N-methyl morpholine (296 ml, 2.66 mmole) in 60 ml THF at

- 230 -

-20°C under N₂ atmosphere was added dropwise isobutyl chloroformate (352 µl, 2.66 mmole). The mixture was stirred at -20°C for 40 minutes, filtered and concentrated *in vacuo* to about 1/4 its volume on a rotary evaporator using no heat. The mixture was cooled to -10°C under N₂ and a freshly prepared ether solution of excess (12 mmole) diazomethane added. After stirring for 18 hours at room temperature, nitrogen was bubbled through the solution for 20 minutes (to remove excess diazomethane) and the mixture concentrated *in vacuo*. The residue was partitioned with methylene chloride-water and the organic phase washed with 5% acetic acid, water, brine, dried over magnesium sulfate and concentrated *in vacuo* to give 1.1 g crude product (oil). Purification by flash chromatography on silica gel in 4:1 methylene chloride:acetone gave 350 mg of the diazoketone (53).

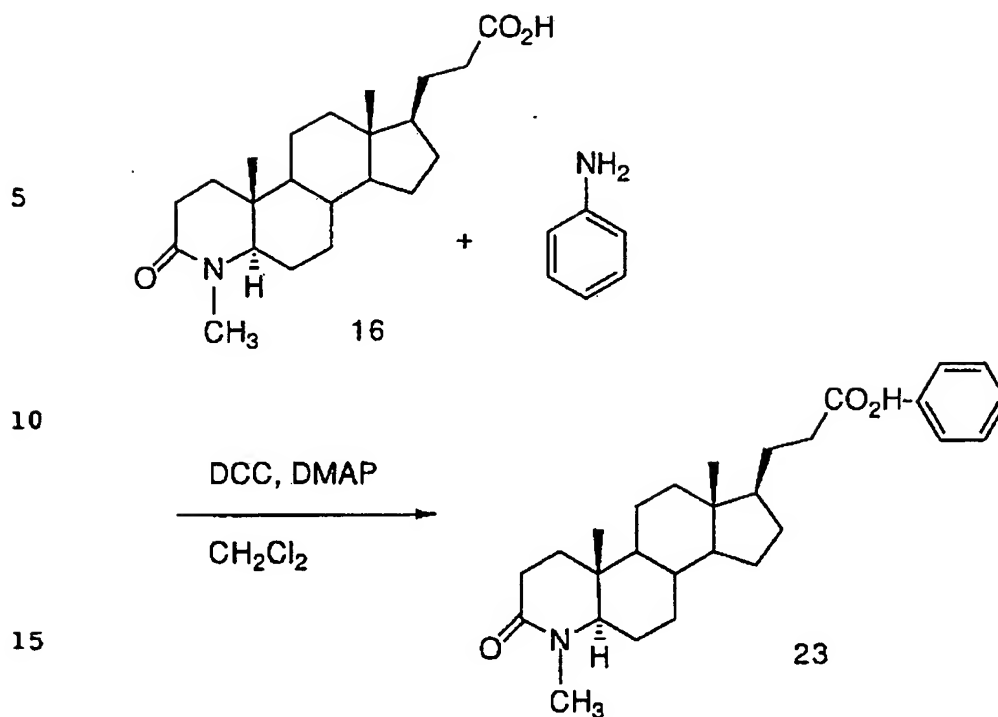
The diazoketone (53), (224 mg, 0.681 mmole) was dissolved in 1 ml of methanol and 266 µl of a 0.218M solution of silver benzoate in triethyl amine (50 mg/ml) was added. The mixture was stirred at room temperature for 2 hours and the dark solution concentrated *in vacuo*. Methylene chloride was added and the mixture filtered. The filtrate was washed with dilute HCl, water, saturated NaHCO₃, brine, dried over magnesium sulfate and concentrated *in vacuo* to give 212 mg crude product (oil). Purification by flash chromatography on silica gel in 4:1 methylene chloride:acetone gave 153 mg of the methyl butyrate (54).

The methyl ester (54) was converted to the free acid (37) using the same conditions as was used in the previous case (52 converted to 17) except that the reflux time was 2 hours.

EXAMPLE 75

3-Oxo-4-methyl-N-phenyl-4-aza-5 α -pregnan-21-carboxamide (23)

- 231 -



To a solution of the acid (16), (57 mg, 0.158 mmole) in
20 2 ml methylene chloride was added 17 μ l (0.190 mmole) aniline, 45
mg (0.220 mmole) dicyclohexylcarbodiimide (DCC) and 1 mg 4-
dimethyl-aminopyridine (DMAP). The mixture was stirred at room
temperature for 5 hours, filtered and concentrated *in vacuo* to give
96 mg crude mixture. Purification by preparative thin layer
25 chromatography on a 1500 μ silica gel plate in 5%
methanol/methylene chloride and trituration with hexane gave 26 mg
of the anilide (23).

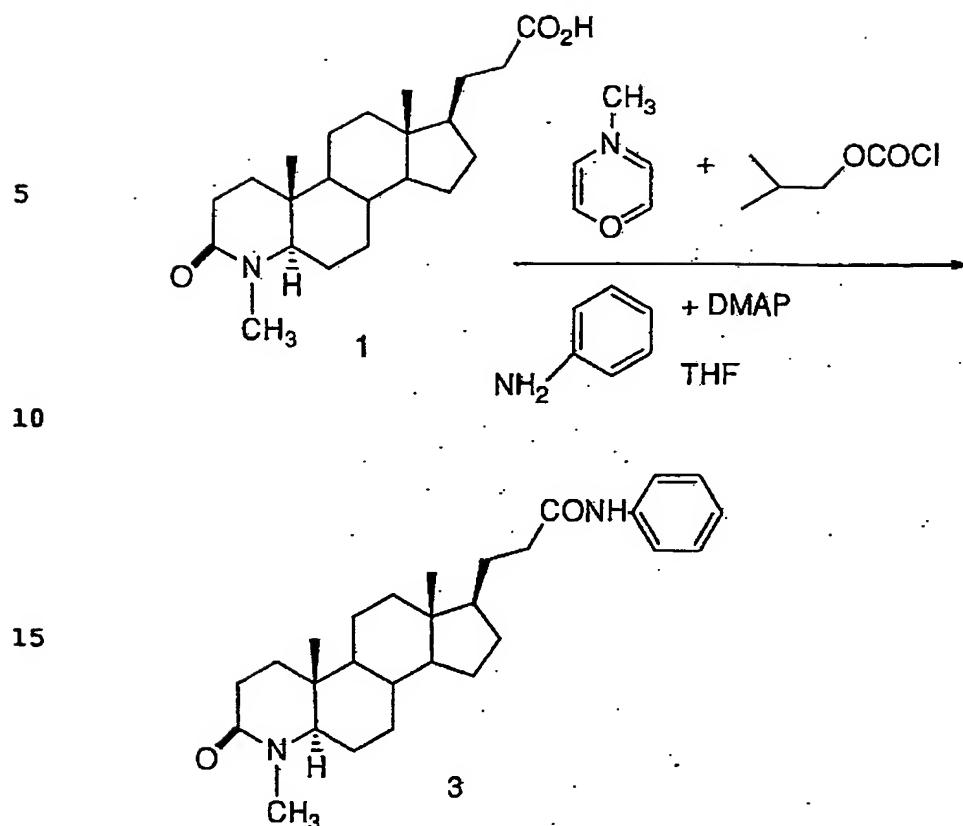
Compounds 18-20, 24-28, 30, 38-39, 42 and 44 were
prepared by the above procedure.

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EXAMPLE 76

3-Oxo-4-methyl-N-phenyl-4-aza-5 α -pregnan-21-amide (3)

- 232 -



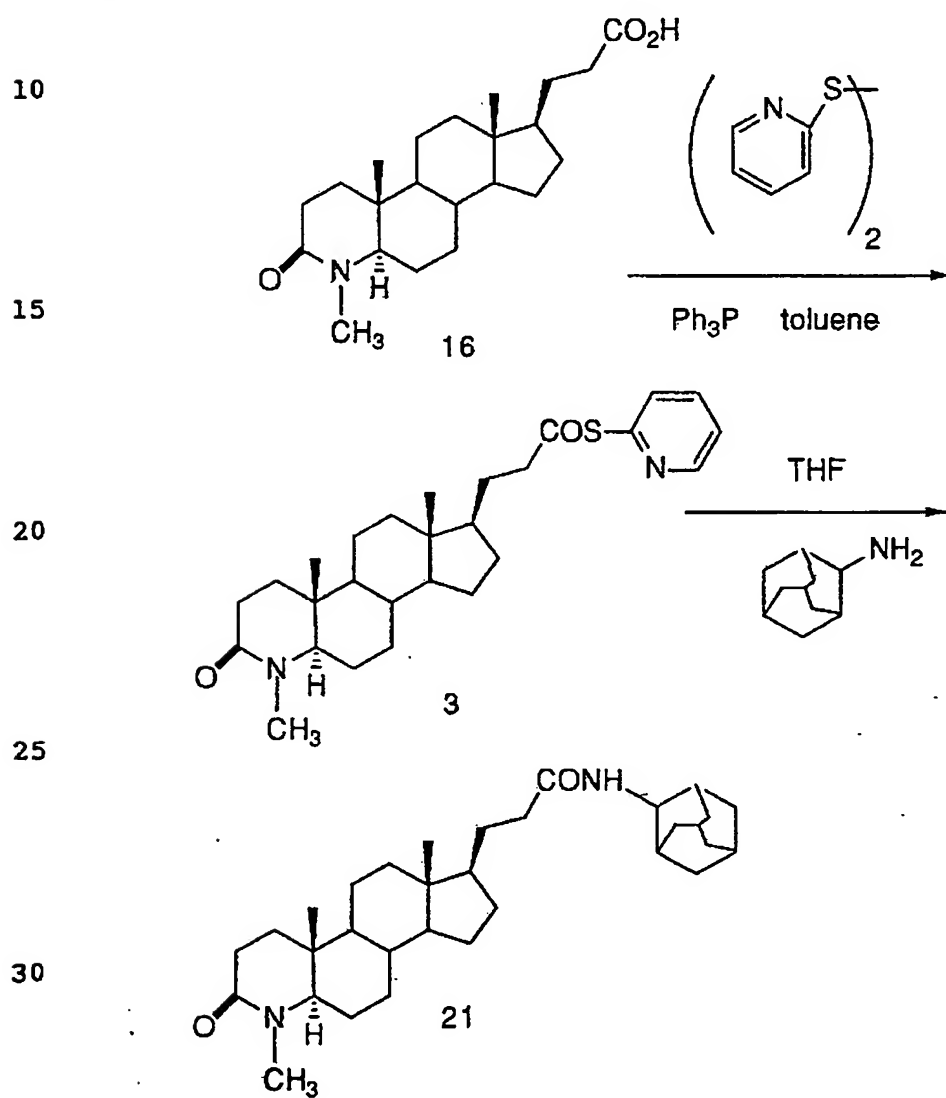
To a solution of the acid (1) (174 mg, 0.50 mmole) and N-methyl morpholine (61 μ l, 0.55 mmole) in 10 ml THF at -20°C under a N_2 atmosphere was added dropwise isobutyl chloroformate (66 μ l, 0.50 mmole). The mixture was stirred at -20°C for 20 minutes and aniline (64 μ l, 0.70 mmoles) plus 4-dimethylaminopyridine (DMAP, 3 mg) was added. The mixture was stirred at -20°C for 30 minutes and then at room temperature for 18 hours. The mixture was concentrated *in vacuo* and the residue partitioned with methylene chloride-water. The organic phase was washed with dilute HCl, water, brine, dried over magnesium sulfate and concentrated *in vacuo* to give 224 mg crude product. Purification by flash chromatography on silica gel in 4:1 methylene chloride:acetone gave 184 mg of the anilide (3).

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Compounds 4-8, 29 and 31 were prepared by the above procedure.

EXAMPLE 77

N-2-adamantyl-3-oxo-4-methyl-4-aza-5 α -pregnan-21-carboxamide
(21)



- 234 -

To a suspension of the acid (16), (391 mg, 1.08 mmole) in 3 ml toluene was added 487 mg (2.16 mmole) 2,2'-dithiodipyridine followed by 567 mg (2.16 mmole) triphenylphosphine. The mixture was stirred at room temperature for 18 hours, concentrated
5 *in vacuo* and the residue flash chromatographed on silica gel in 4:1 methylene chloride:acetone to give a yellow solid. The solid was washed with ether to give 326 mg of the thiopyridyl ester (55).

Using the same procedure, the thiopyridyl esters 56,
10 57, 66 and 83 were prepared from the carboxylic acids 17, 9, 65 and 68 respectively.

To a solution of the thiopyridyl ester (55), (105 mg, 0.231 mmole) in 2.5 ml THF was added 262 mg (1.73 mmole) 2-adamantane amine. The mixture was stirred at room temperature for 18 hours, concentrated *in vacuo* and the residue partitioned with
15 methylene chloride-2N HCl. The organic phase was washed with water, brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was flash chromatographed on silica gel in 4:1 methylene chloride:acetone to give 83 mg of the amide (21).

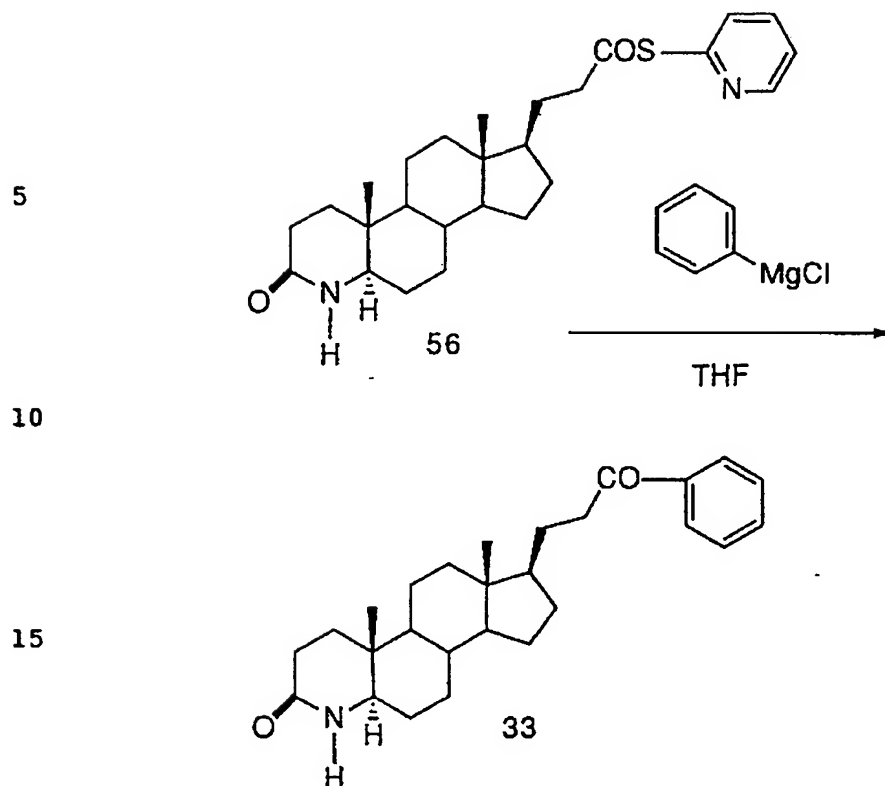
Using the above procedure compounds 14 and 22 were
20 prepared from the thiopyridyl esters 57 and 56 respectively.

EXAMPLE 78

25 21- Benzoyl-4-aza-5 α -pregnan-3-one (33)

30

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To a suspension of the thiopyridyl ester (56), (100 mg, 0.227 mmole) in 4 ml THF at -78°C under a N_2 atmosphere was added phenyl magnesium chloride (250 μl , 0.499 mmole, 2M in THF). The mixture was stirred at -78°C for 45 minutes and allowed to warm to 0°C . The reaction was quenched by the careful addition of 5 drops of brine. The mixture filtered and washed with THF and methylene chloride. The filtrate was concentrated *in vacuo* and the residue dissolved in methylene chloride, washed with 2N NaOH, water, brine, dried over magnesium sulfate and concentrated *in vacuo* to give 84 mg crude mixture. Purification by preparative thin layer chromatography on a 2000 μ silica gel plate in 4:1 methylene chloride:acetone (run up the plate 4 times) gave 20 mg of the phenyl ketone (33).

Compound 32 was prepared by the above procedure.

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EXAMPLE 79

N-(4-Acetylphenyl)-4-methyl-3-oxo-4-aza-5 α -pregnane-20(S)-
carboxamide (15)

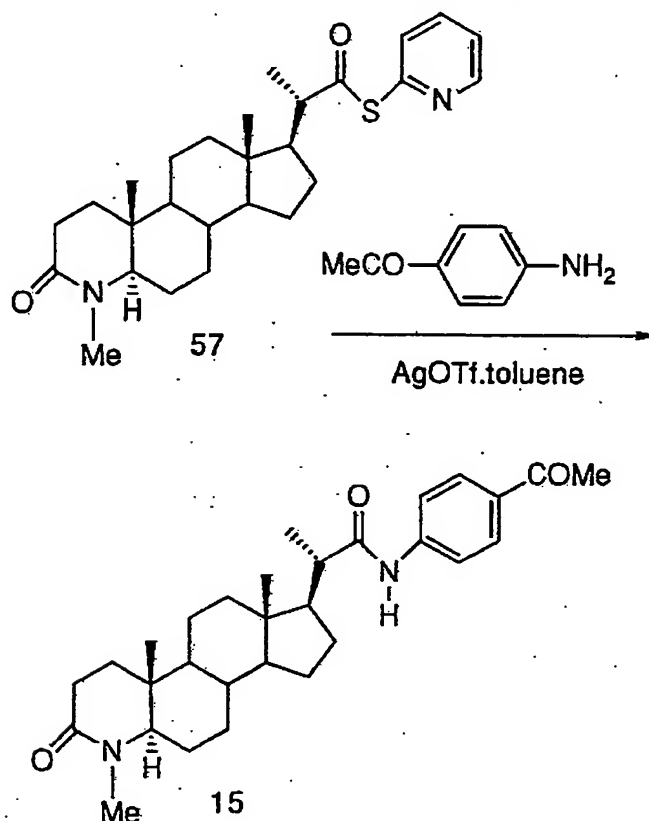
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To a suspension of the thiopyridyl ester (57) (136 mg, 0.3 mmoles) and 4-acetylaniline (81 mg, 0.6 mmoles) in 1.5ml of toluene was added all at once a warm solution of 93 mg (0.36 mmoles) of silver trifluoromethanesulfonate in 0.6 ml of toluene. The suspension was stirred at room temperature for 24 hrs. Periodically the gummy precipitate was dispersed with a glass rod. The suspension was diluted with 30 ml of CH₂Cl₂ and washed with water, 5% ammonium hydroxide, water, and saturated brine and dried (MgSO₄). Evaporation *in vacuo* gave 117 mg of a pale yellow solid. Preparative TLC on two 20x20 cm, 1000 μ , silica gel

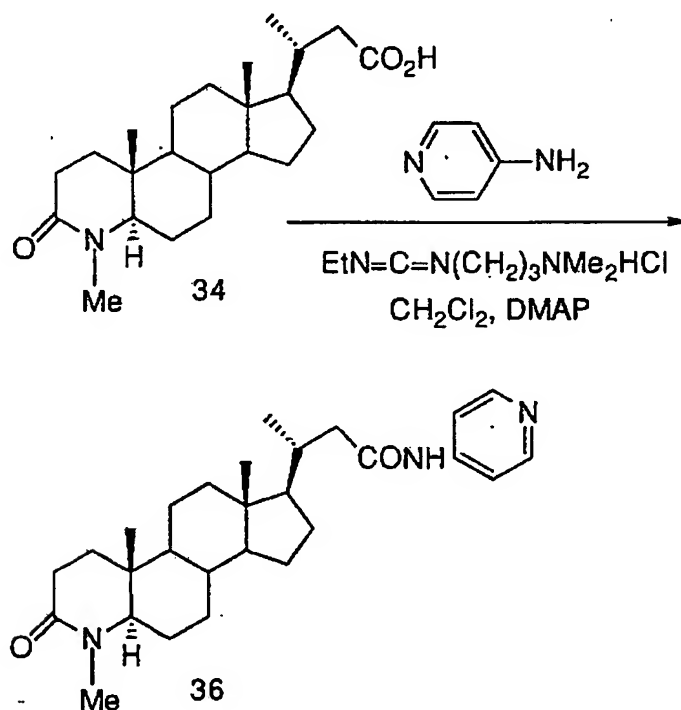
- 237 -

plates with 4:1 CH₂Cl₂-acetone and elution of the strongly UV-active band with 4:1 CH₂Cl₂-MeOH gave 32 mg of pure amide 15.

Compounds 10 and 11 were prepared by the above procedure. Compounds 15a, 15b, 15c, 67, 71, 72, and 77 were prepared by the above procedure except that THF was used instead of toluene.

EXAMPLE 80

4-Methyl-3-oxo-N-(4-pyridyl)-24-nor-4-aza-5 α -cholan-23-amide
(36)



To a solution of 38 mg (0.1 mmole) of the acid 34, 19 mg (0.2 mmoles) of 4-aminopyridine, and 1 mg of 4-dimethyl-amino-pyridine in 0.3 ml of CH₂Cl₂ was added 38 mg (0.2 mmoles)

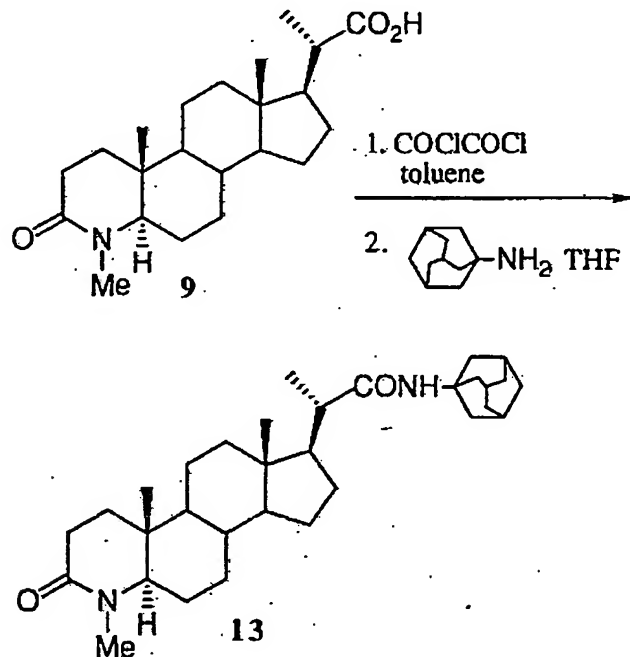
- 238 -

of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The solution was kept at room temperature for 24 hrs, diluted with CH_2Cl_2 , washed with water, dilute K_2CO_3 , water, and saturated brine and dried (MgSO_4). Evaporation *in vacuo* gave 45 mg of a gum. Preparative TLC on a 20x20 cm, 1000 μ silica gel plate with 7% MeOH in CH_2Cl_2 and elution of the strongly UV-active band with 2:1 CH_2Cl_2 -MeOH gave 23 mg of pure amide 36.

Compounds 7a, 8a, 35, 43, 44a, 44b, 44c, 46, 47, 48, 49, 73, 74, 75, 76, 80, 81 and 82 were prepared from the appropriate acids by the above procedure.

EXAMPLE 81

N-(1-Adamantyl)-4-methyl-3-oxo-4-aza-5 α -pregnane-20(S)-carboxamide (13)



To a suspension of 108 mg (0.3 mmoles) of the acid 9 in 1.3 ml of toluene was added 0.24 ml (2.75 mmoles) of oxalyl

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chloride at room temperature. After 30 min the volatiles were removed *in vacuo*, and the residue was dissolved in 1.5 ml of THF. A solution of 181 mg (1.2 mmols) of 1-adamantanamine and 3 mg of 4-dimethyl-aminopyridine in 1 ml of THF was added, and the
5 mixture allowed to stir at room temperature for 20 hrs. Most of the THF was removed *in vacuo*, and the residue partitioned between ice water and CH₂Cl₂. The aqueous phase was extracted with CH₂Cl₂ (2X). The combined organic extracts were washed with 0.5 N HCl, water, and dried (MgSO₄). Evaporation *in vacuo* and flash
10 chromatography of the residue on a 10 mm x 18 cm column of silica gel with 1:1 ethyl acetate-acetone gave 47 mg of pure amide 13.

EXAMPLE 82

15 4-Methyl-3-oxo-24-nor-4-aza-5 α -cholan-23-oic acid (34)

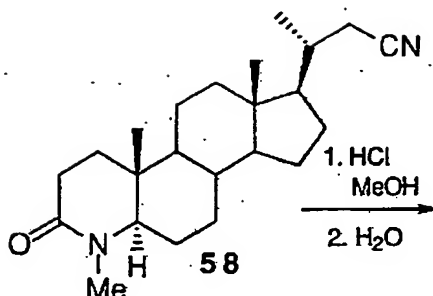
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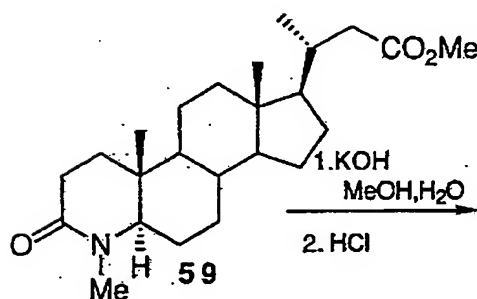
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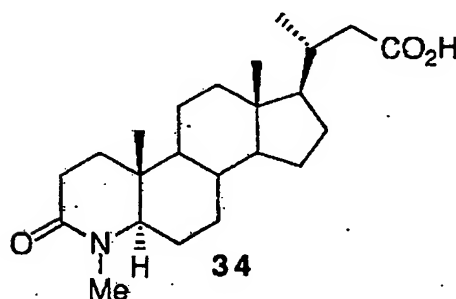


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A solution of 144 mg of 4-methyl-3-oxo-24-nor-4-aza-5 α -cholano-23-nitrile (58, Case 18671) in 5 ml of methanol saturated with anhydrous HCl was allowed to stand at room temperature for 6 hrs. The residue after evaporation *in vacuo* was stirred in 10 ml of water for 3 hrs and extracted with CH₂Cl₂ (3X). The extracts were washed with water and dried (MgSO₄). Evaporation *in vacuo* and flash chromatography of the residue on silica gel with 4:1 CH₂Cl₂-acetone gave 112 mg of methyl 4-methyl-3-oxo-24-nor-4-aza-5 α -cholan-23-oate (59).

30

The methyl ester 59 (101 mg) was saponified to 90 mg of the acid 34 using the procedure in Example 1.

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EXAMPLE 834-Methyl-3-oxo-21-nor-4-aza-5 α -cholane-24-carboxylic acid (45)

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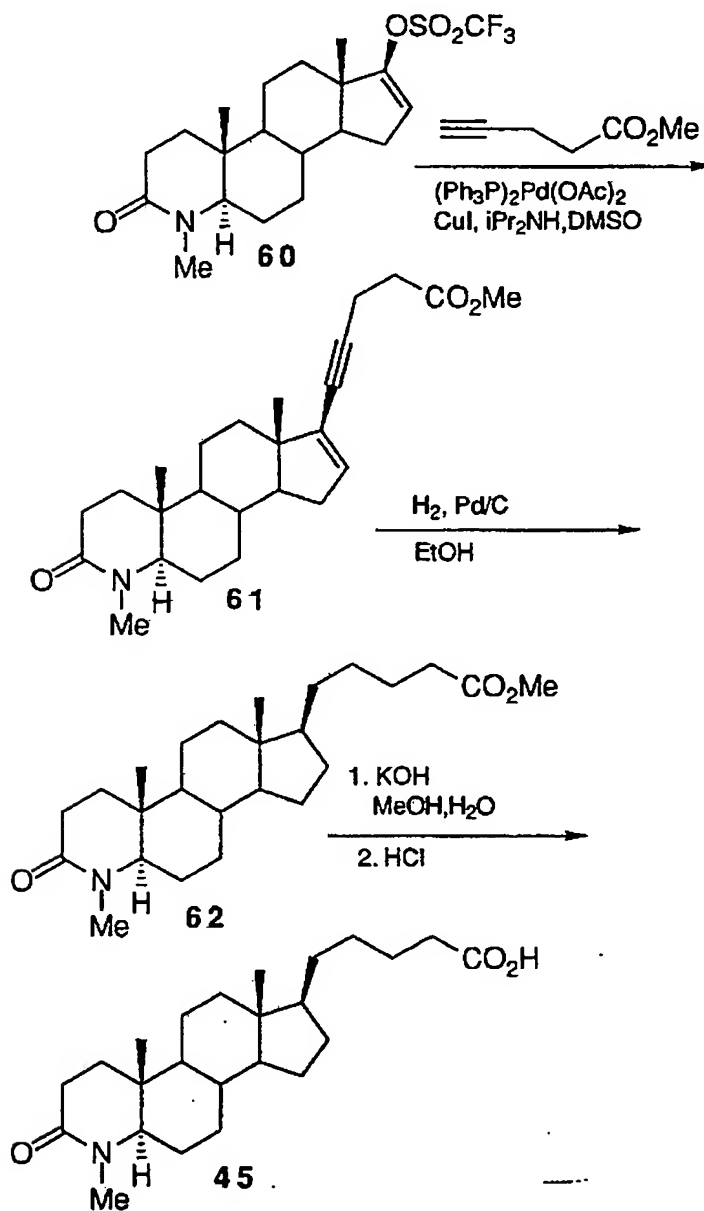
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A mixture of 436 mg (1.0 mmole) of 4-methyl-17-trifluoromethylsulfonyloxy-4-aza-5 α -androst-16-en-3-one (60) (Case 18730), 168 mg (1.5 mmoles) of methyl 4-pentynoate, 40 mg of bis(triphenylphosphine)palladium(II) acetate, 5 mg of cuprous iodide in 3.0 ml of DMSO and 3.0 ml of N,N-diisopropylamine was stirred at room temperature for 17 hrs. The dark reaction mixture was poured into 50 ml of 0.5 M HCl and extracted with CH₂Cl₂ (3X). The combined extracts were washed with water (4X) and dried (MgSO₄). Evaporation *in vacuo* and flash chromatography of the residue on silica gel with 6:1 CH₂Cl₂-acetone gave 400 mg of enyne 61. The enyne was immediately hydrogenated in 20 ml of EtOH with 150 mg of 10% palladium on carbon catalyst under a hydrogen-filled balloon. After stirring at room temperature for 24 hrs, the reaction mixture was filtered through a bed of Celite., which was washed with EtOH (4X). The filtrate and washes were evaporated *in vacuo* and the residue flash chromatographed on silica gel with 5:1 CH₂Cl₂ to give 345 mg of methyl 4-methyl-3-oxo-21-nor-4-aza-5 α -cholane-24-carboxylate (62).

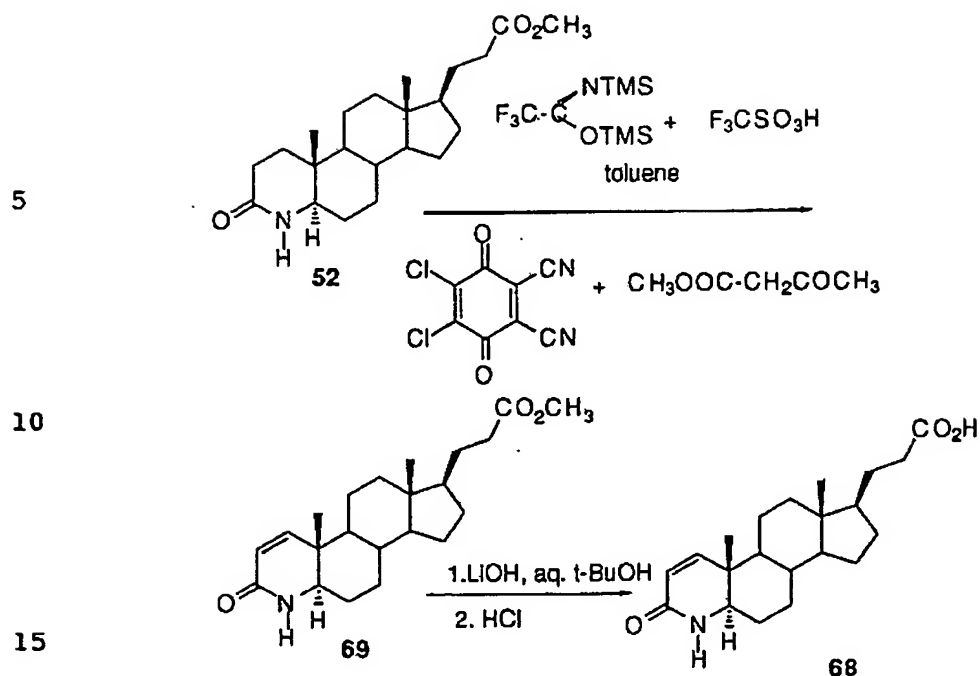
The methyl ester 62 (300 mg) was saponified to 275 mg of the acid 45 using the procedure in Example 1.

The acids 6-(4-methyl-3-oxo-4-aza-5 α -androstan-17 β -yl)hexanoic acid (63) and 11-(4-methyl-3-oxo-4-aza-5 α -androstan-17 β -yl)-undecanoic acid (64) used for the preparation of the anilides 48 and 49 respectively were prepared by the above procedure.

EXAMPLE 84

3-Oxo-4-aza-5 α -pregn-1-ene-21-carboxylic acid

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To a dry toluene solution of the ester **52** (361 mg, 1.0 mmole) under N_2 was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (266 mg, 1.13 mmole), bis(trimethylsilyl)trifluoroacetamide (1.07 ml, 4 mmole) and trifluoromethanesulfonic acid (7 ml, 0.077 mmole) and the clear red solution stirred at room temperature for 24 hours. Methylacetoacetate (11 ml, 0.1 mmole) was added and after stirring for 1 hour at room temperature the solution was refluxed for 24 hours. The reaction mix was concentrated *in vacuo* to a small volume and the residue dissolved in methylene chloride and extracted with an aqueous solution of 1.5% sodium carbonate plus 0.5% sodium sulfite, 5% sodium bicarbonate, dried over magnesium sulfate and concentrated *in vacuo* to give 328 mg crude product. Purification by flash chromatography on silica gel in 9:1 methylene chloride:acetone gave 229 mg of the unsaturated ester **69**.

The unsaturated ester **69** (215 mg, 0.598 mmole) was dissolved in 2 ml *tert*-butanol containing lithium hydroxide monohydrate (75 mg, 1.79 mmole) and 200 ml water and refluxed for 1.5 hours. The mixture was concentrated *in vacuo* to a small volume

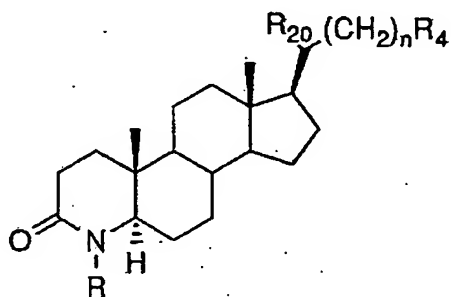
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



and 20 ml water added. The mixture was cooled to 10°C and brought to pH 1 with concentrated HCl. The resulting precipitate was filtered, washed with water, sucked dry and dried in a vacuum oven at 60°C, 25 in. for 18 hours giving 174 mg of the unsaturated acid 68.

Using the above procedures the ester 59a was converted into the ester 79 and the acid 78.

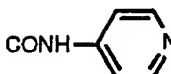
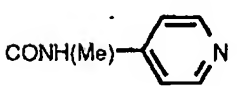
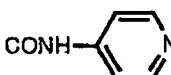
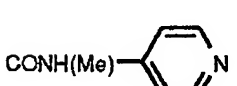
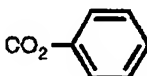
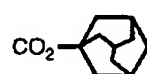

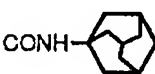
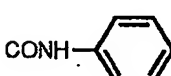
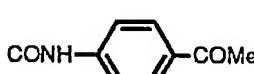
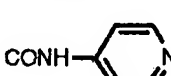
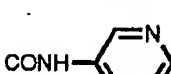
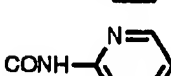
The following tables 6 and 7 list some of the compounds made in this invention and their physical properties. The compound numbers in these two tables are with reference to compounds described in Examples 73 through 84.

Table 6

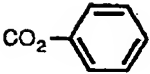
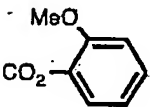
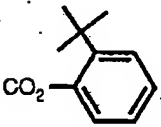
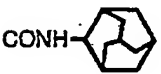
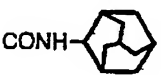
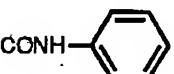
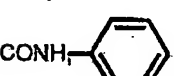
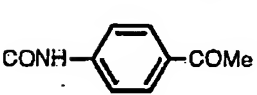

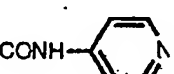
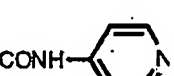
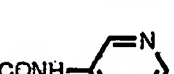
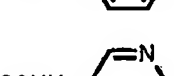
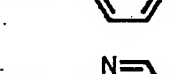


Compd	R	R ₂₀	n	R ₄	NMR
					18-Me
1	Me	H	0	CO ₂ H	
2	H	H	0	CO ₂ H	
3	Me	H	0	CONH- 	0.62
4	H	H	0	CONH- 	0.65
5	H	H	0	CONH- 	0.66
6	H	H	0	CONH- 	0.66

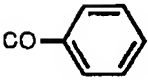
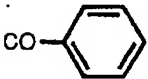
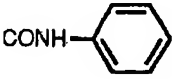
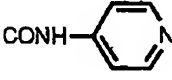
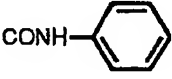
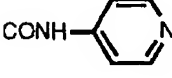
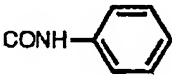
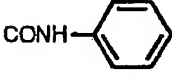
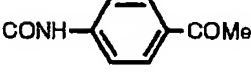
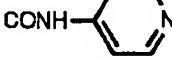
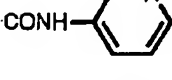
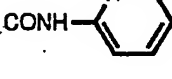
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5	7	Me	H	0		0.64
	7a	Me	H	0		0.44
	8	H	H	0		0.62
	8a	H	H	0		0.45
10	9	Me	Me	0	CO ₂ H	
	10	Me	Me	0		0.76
	11	Me	Me	0		0.67
	12	Me	Me	0		0.68
15	13	Me	Me	0		0.68
	14	Me	Me	0		0.74
	15	Me	Me	0		0.72
	15a	Me	Me	0		0.71
20	15b	Me	Me	0		0.72
	15c	Me	Me	0		0.71
	16	Me	H	1	CO ₂ H	0.60
	17	H	H	1	CO ₂ H	

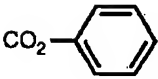
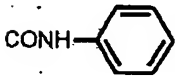
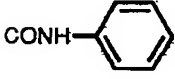
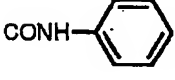
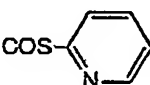
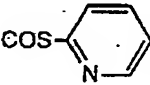
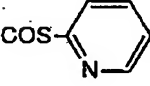
- 246 -

5	18	Me	H	1		0.65
	19	Me	H	1		0.64
	20	Me	H	1		0.65
10	21	Me	H	1		0.62
	22	H	H	1		0.62
	23	Me	H	1		0.63
15	24	H	H	1		0.63
	25	Me	H	1		0.63
	26	H	H	1		0.63
20	27	Me	H	1		0.64
	28	H	H	1		0.63
	29	Me	H	1		0.63
25	30	H	H	1		0.62
	31	Me	H	1		0.62

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5	32	Me	H	1		0.64
	33	H	H	1		0.63
	34	Me	Me	1	CO ₂ H	0.69
	35	Me	Me	1		0.73
10	36	Me	Me	1		0.71
15	37	Me	H	2	CO ₂ H	0.58
	38	Me	H	2		
	39	Me	H	2		0.59
	40	Me	Me	2	CO ₂ H	
20	41	H	Me	2	CO ₂ H	0.65
25	42	Me	Me	2		0.68
	43	H	Me	2		0.69
	44	Me	Me	2		0.68
	44a	Me	Me	2		0.66
30	44b	Me	Me	2		0.66
	44c	Me	Me	2		0.67
	45	Me	H	3	CO ₂ H	0.55

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5	46	Me	H	3		0.57
	47	Me	H	3		0.56
	48	Me	H	4		0.55
	49	Me	H	9		0.56
10	52	H	H	1	CO ₂ Me	0.61
	53	Me	H	1	COCHN ₂	
	54	Me	H	2	CO ₂ Me	0.58
	55	Me	H	1		0.62
15	56	H	H	1		0.64
	57	Me	Me	0		0.74
	58	Me	Me	1	CN	
	59	Me	Me	1	CO ₂ Me	0.70
25	59a	H	Me	2	CO ₂ Me	0.64
	62	Me	H	3	CO ₂ Me	0.56
	64	Me	H	9	CO ₂ H	0.56

30

Table 6, part 2

Compd NMR
19-Me

OtherMass Spectrum

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	1	J. Med. Chem. 1984, 27, 1690-1701.		
	2			m/e334(M+1) FAB
5	3	0.84	7.04-7.52 (m, 5H, ArH)	m/e423(M+1) FAB
	4	0.91	7.07-7.53 (m, 5H, ArH)	m/e409(M+1) FAB
	5	0.90	2.58(s, 3H, COMe); 7.61(d, 2H, ArH); 7.94(d, 2H, ArH)	m/e466(M+2) FAB
10	6	0.90	2.57(s, 3H, COMe); 7.62(d, 2H, ArH); 7.93(d, 2H, ArH)	m/e451(M+1) FAB
	7	0.90	7.56(d, 2H, ArH); 8.46(d, 2H, ArH)	m/e424(M+1) FAB
15	7a	0.85	3.30(s, 3H, NMe); 7.13(d, 2H, ArH); 8.65(d, 2H, ArH)	
	8	0.88	7.58(d, 2H, ArH); 8.44(d, 2H, ArH)	m/e410(M+1) FAB
20	8a	0.87	3.27(s, 3H, NMe); 7.15(d, 2H, ArH); 8.66(d, 2H, ArH)	m/e423(M) EI
	9	J. Med. Chem. 1984, 27 1690-1701		
	10	0.91	1.36(s, 3H, 21-Me); 7.0-7.5(m, 5H, ArH)	
25	11	0.88	1.13(d, 3H, 21-Me); 1.64, 2.09, 2.14(bs, 15H, adamantylH);	
	12	0.90	1.03(s, 9H, CMe3); 1.12(d, 3H, 21-Me); 1.40, 1.42(s, 6H, NCMe2); 5.20(s, 1H, NH)	
30	13	0.89	1.14(d, 3H, 21-Me); 1.67, 1.99, 2.06(bs, 15H, adamantylH); 5.03(bs, 1H, NH)	
	14	0.90	1.28(d, 3H, 21-Me); 7.06- 7.70(m, 5H, ArH)	
	15	0.89	1.28(d, 3H, 21-Me); 2.58(s, 3H, COMe); 7.68(d, 2H, ArH); 7.92(d, 2H, ArH); 8.00(bs, 1H, NH)	

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5	15a	0.89	1.27(d,3H,21-Me); 7.64(d,2H,ArH); 8.44(d,2H,ArH); 8.50(s,1H,NH)		
	15b	0.89	1.29(d,3H,21-Me); 7.28(m,1H,ArH); 7.92(s,1H,ArH); 8.30(m,2H,ArH); 8.61(bs,1H,NH)		
	15c	0.88	1.28(d,3H,21-Me); 7.04(m,1H,ArH); 7.78(m,1H,ArH); 8.13(m,3H,ArH+NH)		
10	16	0.90		m/e361(M)	EI
	17			m/e347(M)	EI
	18	0.90	7.05-7.41(m,5H,ArH)	m/e437(M)	EI
15	19	0.89	3.81(s,3H,OMe); 6.90-7.29(m,4H,ArH)		
	20	0.90	1.35(s,9H,CMe ₃); 6.95- 7.43(m,4H,ArH)		
	21	0.90		m/e495(M+1)	FAB
20	22	0.91		m/e481(M+1)	FAB
	23	0.89	7.05-7.54(m,5H,ArH)	m/e436(M)	EI
	24	0.91	7.06-7.55(m,5H,ArH)	m/e422(M)	EI
25	25	0.89	2.56(s,3H,COMe); 7.64(d,2H,ArH); 7.93(d,2H,ArH)	m/e478(M)	EI
	26	0.91	2.57(s,3H,COMe); 7.63(d,2H,ArH); 7.91(d,2H,ArH)	m/e464(M)	EI
	27	0.90	7.84(d,2H,ArH); 8.43(d,2H,ArH)	m/e437(M)	EI
30	28	0.91	7.58(d,2H,ArH); 8.46(d,2H,ArH)	m/e424(M+1)	FAB
	29	0.89	7.30(m,1H,ArH); 8.28(m,2H,ArH); 8.60(s,1H,ArH)		

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	30	0,90	7.33(m,1H,ArH); 8.32(m,2H,ArH); 8.62(s,1H,ArH)	m/e424(M+1) FAB
	31	0.89	7.05(m,1H,ArH); 7.31(m,1H,ArH); 8.24(m,2H,ArH)	
5	32	0.91	7.38-7.62(m,3H,ArH); 7.95(d,2H,ArH)	
	33	0.90	7.05-7.54(m,5H,ArH)	m/e408(M+1) FAB
	34	0.86	1.01(d,2H,21-Me)	
10	35	0.89	1.04(d,3H,21-Me); 7.03- 7.62(m,5H,ArH); 7.21(bs,1H,NH)	
	36	0.87	1.01(d,3H,21-Me); 7.60(bs,2H,ArH); 8.40(s,1H,NH); 8.44(bs,2H,ArH)	
	37	0.90		m/e376(M+1) FAB
15	38	0,87	7.07-7.49(m,5H,ArH)	m/e451(M+1) FAB
	39	0,89	7.58(d,2H,ArH); 8.46(d,2H,ArH)	m/e451(M+1) FAB
	40		J. Med. Chem. 1986, 29 2298-2315	
20	41	0.88	0.91(d,3H,21-Me)	
	42	0.89	0.96(d,3H,21-Me); 7.03- 7.56(m,5H,ArH); 7.48(bs,1H,NH)	
	43	0.91	0.96(d,3H,21-Me); 5.92(bs,1H,NH); 7.04-7.64(m,5H,ArH)	
25	44	0.89	0.96(d,3H,21-Me); 2.57(s,3H,COMe); 7.66(d,2H,ArH); 7.90(d,2H,ArH); 8.16(bs,1H,NH)	
	44a	0.88	0.94(d,3H,21-Me); 7.60(d,2H,ArH); 8.37(s,1H,NH); 8.44(d,2H,ArH)	
30	44b	0.88	0.96(d,3H,21-Me); 7.33(m,1H,ArH); 8.02(bs,1H,ArH); 8.33(m,2H,ArH); 8.64(s,1H,NH)	
	44c	0.87	0.95(d,3H,21-Me); 7.08(m,1H,ArH); 7.78(m,1H,ArH); 8.25(m,2H,ArH); 8.68(bs,1H,NH)	
	45	0.87	2.31(t,2H,CH ₂ CO ₂)	

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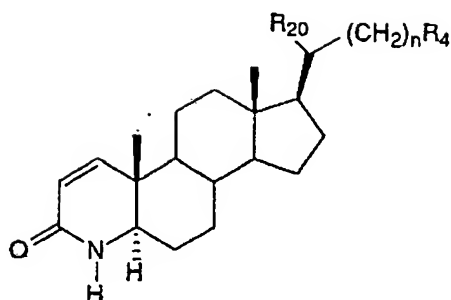
	46	0.88	2.53(t,2H,CH ₂ CO ₂); 7.02-7.38(m,5H,ArH)
	47	0.87	2.33(t,2H,CH ₂ CO ₂); 7.05-7.52(m,5H,ArH); 7.21(s,1H,NH)
5	48	0.87	2.33(t,2H,CH ₂ CO ₂); 7.05-7.52(m,5H,ArH); 7.23(s,1H,NH)
	49	0.88	2.33(t,2H,CH ₂ CO ₂); 7.05-7.54(m,5H,ArH)
	52	0.90	3.66(s,3H,OMe); 5.83(bs,1H,NH)
10	53		IR, 2140 cm ⁻¹ N ₂
	54	0.90	2.30(t,2H,CH ₂ CO ₂); 3.69(s,3H,OMe)
	55	0.90	7.30(m,1H,ArH); 7.70(m,2H,ArH); 8.62(m,1H,ArH)
15	56	0.92	5.7(bs,1H,NH); 7.31(m,1H,ArH); 7.71(m,2H,ArH); 8.63(m,1H,ArH)
	57	0.90	1.32(d,3H,21-Me); 7.32(m,1H,ArH); 7.72(m,2H,ArH); 8.63(m,1H,ArH)
	59	0.88	0.97(d,3H,21-Me); 3.65(s,3H,OMe)
20	59a	0.88	0.91(d,3H,21-Me); 3.65(s,3H,OMe); 5.77(s,1H,NH)
	62	0.88	2.29(t,2H,CH ₂ CO ₂); 3.66(s,3H,OMe)
	64	0.86	2.33(t,2H,CH ₂ CO ₂)

25

Table 7

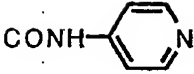
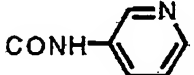
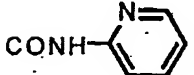
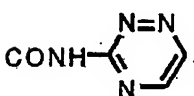
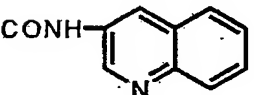
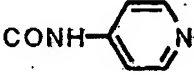
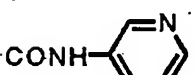
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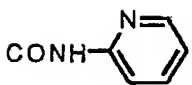
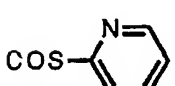


	Compd	R20	n	R4	NMR		Other
					18-Me	19-Me	
5	65	Me	0	CO2H			
10	66	Me	0		0.63	0.95	1.33(d,3H,21-Me); 5.81(d,1H,1-H); 6.03(bs,1H,NH); 6.79(d,1H,2-H); 7.34, 7.63, 7.79, 8.64(m,1H ea,ArH)
15	67	Me	0		0.72	0.94	1.25(d,3H,21-Me); 5.78(d,1H,1-H); 6.79(d,1H,2-H); 7.62(d,2H,ArH); 8.39(d,2H,ArH)
20	68	H	1	CO2H	0.57	0.87	5.59(d,1H,1-H); 6.82(d,1H,2-H)
	69	H	1	CO2Me	0.62	0.98	3.66(s,3H,OMe); 5.82(d,1H,1-H); 6.82(d,1H,2-H);
25	70	H	1		0.64	0.98	5.81(d,1H,1-H); 6.82(d,1H,2-H); 7.05-7.54(m,5H,ArH)
	71	H	1		0.64	0.97	3.79(s,3H,OMe); 5.82(d,1H,1-H); 6.82(d,1H,2-H); 6.86(d,2H,ArH); 7.42(d,2H,ArH)
30	72	H	1		0.62	0.97	5.81(d,1H,1-H); 6.81(d,1H,2-H); 6.78(s,2H,ArH)

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5	73	H	1		0.64	0.97	5.78(d,1H,1-H); 6.83(d,1H,2-H); 7.58(d,2H,ArH); 8.39(d,2H,ArH)
	74	H	1		0.63	0.96	5.79(d,1H,1-H); 6.79(d,1H,2-H); 7.28(m,1H,ArH); 8.27(m,2H,ArH); 8.58(s,1H,ArH)
	75	H	1		0.64	0.98	5.81(d,1H,1-H); 6.81(d,1H,2H); 7.04(m,1H,ArH); 7.96(m,1H,ArH); 8.24(m,2H,ArH)
	76	H	1		0.64	0.97	5.81(d,1H,1-H); 6.80(d,1H,2-H); 8.51(d,1H,ArH); 8.96(d,1H,ArH)
	77	H	1		0.64	0.95	5.82(d,1H,1-H); 6.86(d,1H,2-H); 7.52-8.06(m,4H,ArH); 8.71-8.95(m,2H,ArH)
20	78	Me	2	CO ₂ H	0.63	0.83	0.87(d,3H,21-Me); 5.59(d,1H,1-H); 6.78(d,1H,2-H);
	79	Me	2	CO ₂ Me	0.66	0.95	0.91(s,3H,21-Me); 3.64(s,3H,OMe); 5.41(s,1H,4-NH); 5.78(d,1H,1-H); 6.77(d,1H,2-H)
25	80	Me	2		0.68	0.97	0.95(d,3H,21-Me); 5.46(s,1H,4-NH); 5.81(d,1H,1-H); 6.80(d,1H,2-H); 7.56(d,2H,ArH); 8.13(bs,1H,CONH); 8.46(d,2H,ArH)
30	81	Me	2		0.68	0.96	0.94(d,3H,21-Me); 5.58(bs,1H,4-NH); 5.81(d,1H,1-H); 6.80(d,1H,2-H); 7.24(m,1H,ArH); 8.03(m,1H,ArH); 8.22(d,1H,ArH); 8.32(bs,1H,ArH); 8.58(bs,1H,CONH)

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5	82	Me 2		0.69	0.96	0.97(d,3H,21-Me); 5.54(bs,1H,4-NH); 5.81(d,1H,1-H); 6.79(d,1H,2-H); 7.08(m,1H,ArH); 7.76(m,1H,ArH); 8.26(m,2H,ArH); 8.71(bs,1H,CONH)
	83	H 1		0.62	0.97	5.80(d,1H,1-H); 6.80(d,1H,2-H); 7.18-7.78(m,3H,ArH); 8.60(d,1H,ArH)

10

Table 7, part 2

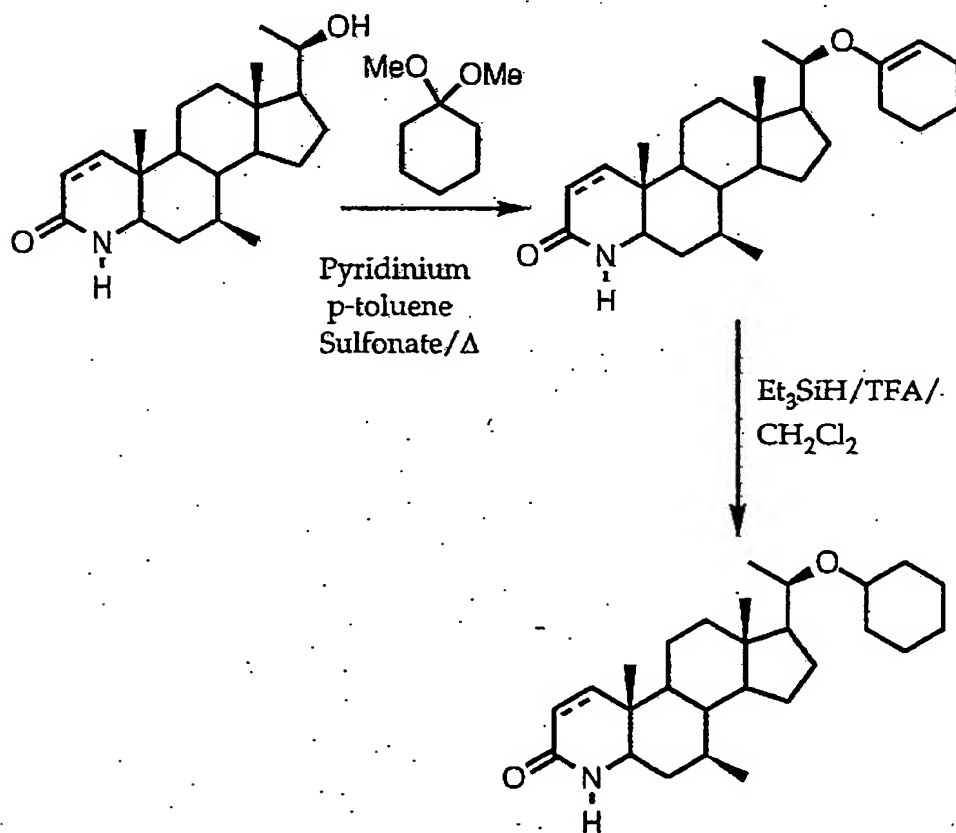
	Compd	Mass Spectrum
15	69	m/e359(M+) EI
	70	m/e420(M+) EI
20	71	m/e451(M+1)) FAB
	72	m/e410(M+) EI
25	73	m/e421(M+) EI
	74	m/e422(M+1)) FAB
30	75	m/e422(M+1)) FAB
	76	m/e423(M+) EI

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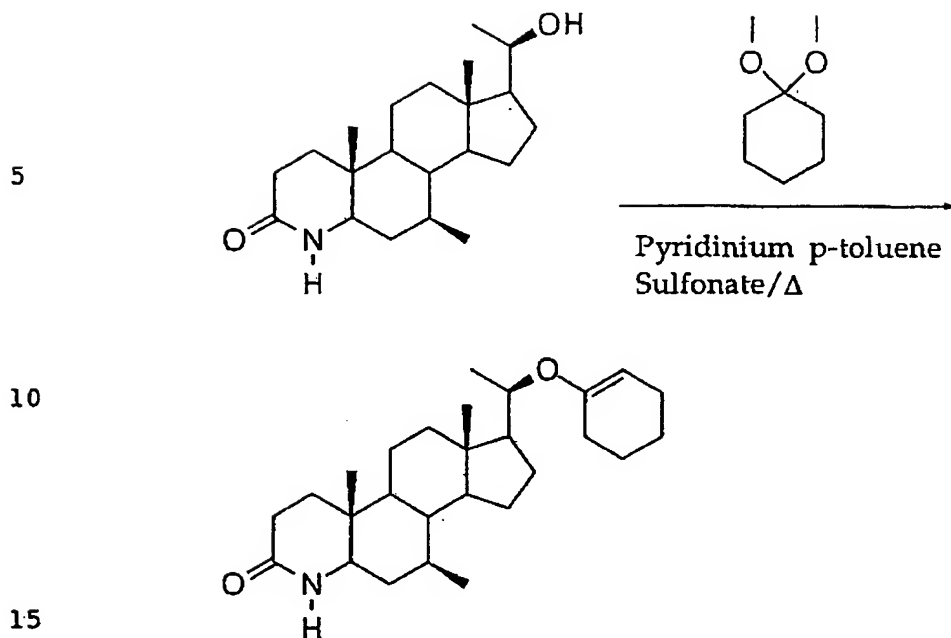
77 m/e472(M+1)
) FAB

Another preferred embodiment of this invention is a series of compounds characterized in having ether moieties at the 17 position, and which can be synthesized according to the following flowsheet:

Flowsheet XXXIII

EXAMPLE 85

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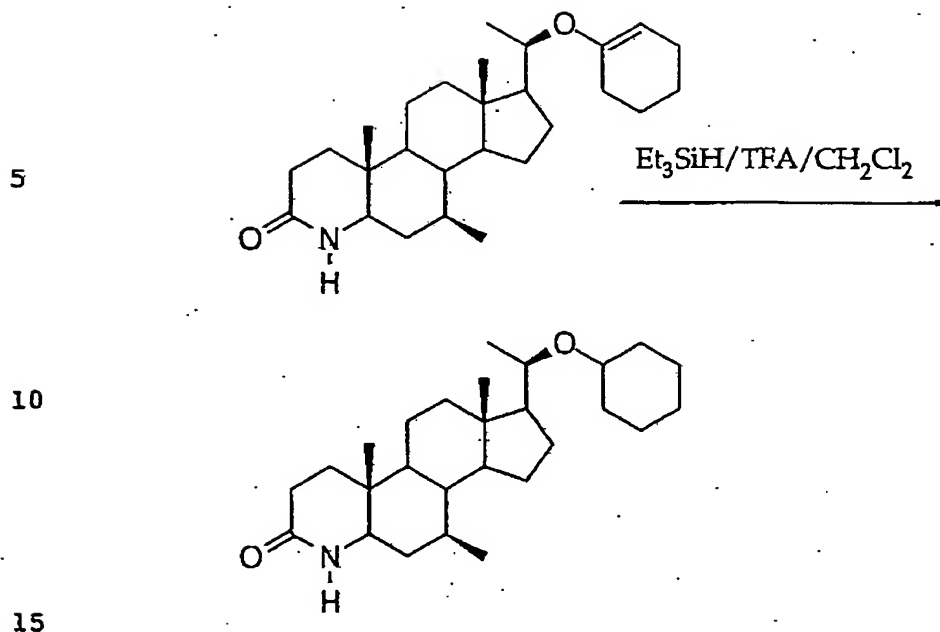


To a solution of Azasteroid (250mg) in dimethoxycyclohexane (10ml) was added pyridinium p-toluenesulfonate and reaction mixture was heated at 140° for 2hrs. The temperature of reaction was increased and dimethoxycyclohexane was removed slowly by distillation over 4hrs. Finally all the dimethoxycyclohexane was distilled off and residue taken in ethyl acetate, washed with aqueous sodium bicarbonate, brine, dried and concentrated to give 2. MS calculated for C₂₇H₄₃NO₂, 413.65. Observed 413 (EI).

EXAMPLE 86

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To a solution of Enol Ether (150 mg) in CH_2Cl_2 (2ml) was added triethylsilane (418.6 mg, 10 eq.) followed by slow dropwise addition of TFA (2.07g). After stirring the reaction for overnight at room temperature, the reaction mixture was diluted with CH_2Cl_2 , washed with aq. NaHCO_3 , brine, dried and concentrated. The residue was purified by prep. tlc over silica gel using 30% acetone/ CH_2Cl_2 as solvent. MS calculated for $\text{C}_{27}\text{H}_{45}\text{NO}_2$, 415.66. Observed 415(EI).

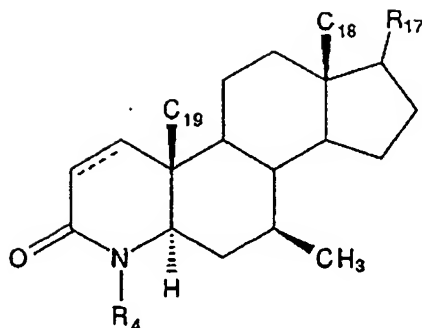
25 An additional preferred embodiment of the invention is presented in the following Table 8, in which compounds are presented that are readily synthesizable by one of ordinary skill in this art by following the procedures previously presented and exemplified:

Table 8.

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10 Example R₄
No.

R₁₇

87	CH ₃	β-(R)-CH(CH ₃)(CH ₂) ₃ CH(CH ₃) ₂
88	CH ₃	β-COCH ₃
15 89	CH ₃	β-(E)-C(CH ₃)=CH(4-Pyridyl)
90	CH ₃	β-(S)-CH(CH ₃)CH ₂ CN
91	CH ₃	β-(R)-CH(CH ₃)CH ₂ CN
92	CH ₃	β-(CH ₂) ₂ CF ₃
93	CH ₃	β-OCONHCH(CH ₃) ₂
94	CH ₃	β-(CH ₂) ₂ CO ₂ -Ph
20 95	CH ₃	β-(CH ₂) ₂ -(1-Phenyltetrazol-5-yl)
96	CH ₃	β-(CH ₂) ₂ -(2-Methyl-1,3,4-oxadiazol-5-yl)
97	CH ₃	β-CH ₂ CONH-(4-Pyridyl)
98	CH ₃	β-CH ₂ CH ₃
99	CH ₃	Δ ¹⁶
25 100	CH ₃	17-H
101	Me	3-thiophenecarboxamido
102	Me	2-methyl-3-fluorobenzamido
103	Me	phenylthioacetamido
104	Me	t-butylthioacetamido
105	Me	phenylthioacetamido
30 106	Me	2-fluorobenzamido
107	Me	2-thiophenesulfonamido
108	Me	2,3-difluorobenzamido
109	Me	isopropylthioacetamido
110	Me	O-((isopropylthio)acetyl)oximino
111	Me	9-(isopropylthio)nonanoylamido

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	112	Me	β -O-phenyl-p-cyano
	113	Me	β -O-CH ₂ COOEt
	114	Me	β -O-CH ₂ COOH
	115	Me	β -O-CH ₂ CONHPh
5	116	Me	β -O-CH ₂ CONHPh-p-COMe
	117	Me	exo-methylene
	118	Me	17 α -OH, 17 β -CH ₂ N ₃
	119	Me	β -Me
	120	Me	α -OH, β -CH ₂ NHCMe ₃
	121	Me	α -OH, β -CH ₂ NH ₂
10	122	Me	cyclopropyl-16-ene

Table 8, part 2

		C18	C19	7 β -CH ₃	other	¹³ C	M ⁺ or M+1 ⁺
15	87	0.93	0.89	1.15 d	1.2 d	63-65	415 (M ⁺)
	88	0.63	0.85	1.06 d	2.13(s,3H,COMe)		
	89	0.64	0.84	1.09 d	1.91(s,3H,C=CMe); 6.23(s,1H,C=CH); 7.17(bs,2H,ArH); 8.55(bs,2H,ArH)		
	90	0.71	0.85	1.05 d	1.19(d,3H,21-Me)		
20	91	0.70	0.84	1.05 d	1.08(d,3H,21-Me)		
	92	0.62	0.85	1.06 d			
	93	0.76	0.84	1.04 d	1.15(d,6H,CHMe ₂); 4.49(t,1H,17-H)		
	94	0.64	0.84	1.05 d	7.04-7.39(m,5H,Ar)		451(M ⁺)
	95	0.56	0.85	1.04 d	7.43-7.63(m,5H,Ar)		476(M+1) ⁺
	96	0.63	0.85	1.05 d	2.49(s,3H,C(CH ₃)=N)		413(M ⁺)
25	97	0.64	0.86	1.06 d	7.54(d,2H,Ar); 8.48(d,2H,Ar)		437(M ⁺)
	98	0.55	0.83	1.02 d	0.84 (t, 3H, CH ₃)		332 (M ⁺)
	99	0.74	0.85	1.04 d	5.65 (m, 1H, 16-H); 5.78 (m, 1H, 17H)		
	100	0.70	0.83	1.05 d	2.92 (s, 3H, N-Me)		304 (M ⁺)
	101	0.755	0.833	1.033	2.904(N-Me)		M+ = 428
	102	0.76	0.85	1.04	2.82 (N-Me)		M+ = 454
30	103	0.441	0.784	0.975	2.879 (N-Me)		M+ = 468
	104	0.719	0.820	1.011	2.891 (N-Me)		M+ = 448
	105	0.446	0.784		2.879 (N-Me)		M+ = 524
	106	0.777	0.839	1.037	2.907 (N-Me)		M+1 = 440
	107	0.688	0.812	0.975	2.884 (N-Me)		M+ = 464
	108	0.799	0.858	1.048	2.923 (N-Me)		M+ = 458
	112	0.88	0.94	1.07	2.93 (N-Me), 4.14 (t, 17 α)	200-202	M ⁺ = 420

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	113	0.82	0.86	1.05	2.92, 3.38 (t, 17 α), 4.09 (OCH ₂)		M ⁺ = 405
	114	0.84	0.86	1.05	2.92, 3.42 (t, 17 α), 4.10 (OCH ₂)	163-166	M+1 ⁺ = 378
5	115	0.88	0.89	1.06	2.92, 3.42 (t, 17 α), 4.06 (OCH ₂)	175.5-178.5	M+1 ⁺ = 453
	116	0.89	0.90	1.07	2.58 (MeCO), 2.93, 3.44 (t, 17 α), 4.07 (OCH ₂)	212-216	M+1 ⁺ = 495
	117	0.82	0.88	1.10	2.92, 4.67 (m, =CH ₂)	85-87.5	M ⁺ = 315
10	118	0.78	0.88	1.07	2.93, 3.49 (ABq, CH ₂ N)	243.5-246	M+1 ⁺ = 375
	119	0.57	0.87	1.06	0.83 (d, 17 β -Me)	98-100	M ⁺ = 318
	120	0.75	0.89	1.07	1.28 (CMe ₃), 2.76 (ABq, CH ₂ N)		M ⁺ = 404
	121	0.76	0.87	1.09		272-277	M ⁺ = 348
15	122	0.83	0.89	1.06	0.39 (m, 2H, cyclopropyl), 0.64 (m, 2H,cyclopropyl), 5.11 (m, =CH-)		M ⁺ = 341

In this specifications, R_f values cited were carried out on standard thin layer chromatographic Silica gel plates. The elution solvent system used is given in the parentheses following the R_f value.

The mass spectral values cited are given as FAB, i.e., fast atom bombardment, and are reported as (M+1) molecular ion peaks, being the molecular weight plus one atomic mass unit. The electron impact (EI) mass spectrum values cited are reported as molecular ion peaks and are indicated in parentheses, either being (M) or (M+2), the molecular weight, MW, or the MW plus two atomic units.

The nuclear magnetic resonance data was taken at 400 MHz in CDCl₃ and is tabulated for representative unique proton values. The coupling constant J is given in Hertz, Hz.

The present invention has the objective of providing suitable topical, oral and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention.

The compositions containing the compounds of the present invention as the active ingredient for use in the treatment of

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e.g., benign prostatic hypertrophy, prostatitis, and treatment and prevention of prostatic carcinoma, hyperandrogenic conditions, can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration, as, for example,
5 by oral administration in the form of tablets, capsules, solutions, or suspensions, or by injection. The daily dosage of the products may be varied over a wide range varying from 0.5 to 1,000 mg per adult human/per day. The compositions are preferably provided in the
10 form of scored tablets containing 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, and 50.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.002 mg. to about 50 mg./kg. of body weight per day. Preferably the range is from about 0.01 mg. to 7 mg./kgs. of body
15 weight per day. These dosages are well below the toxic dose of the product. For the treatment of androgenic alopecia, acne vulgaris, seborrhea, female hirsutism, the compounds of the present invention are administered in a pharmaceutical composition comprising the active compound in combination with a pharmacologically acceptable
20 carrier adapted for topical, oral or parenteral administration.

These topical pharmaceutical compositions may be in the form of a cream, ointment, gel or aerosol formulation adapted for application to the skin. These topical pharmaceutical compositions containing the compounds of the present invention ordinarily include
25 about 0.1% to 15%, preferably about 5%, of the active compound, in admixture with about 95% of vehicle.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills,
30 powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

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An effective but non-toxic amount of the compound desired can be employed as a 5 α -reductase agent.

5 The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or
10 veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a
15 consideration of the distribution, equilibrium, and elimination of a drug.

Oral dosages of the present invention, when used for the indicated effects, will range between about Advantageously, compounds of the present invention may be administered in a single daily dose, or
20 the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill
25 in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds
30 herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

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For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, 5 suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes 10 and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

15 The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

20 Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran 25 copolymer, polyhydroxypropyl-methacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic 30 acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

BIOLOGICAL ASSAYS

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Preparation of Human prostatic and scalp 5 α -reductases.

Samples of human tissue were pulverized using a freezer mill and homogenized in 40 mM potassium phosphate, pH 6.5, 5 mM magnesium sulfate, 25 mM potassium chloride, 1 mM phenylmethyl-sulfonyl fluoride, 1 mM dithiothreitol (DTT) containing 0.25 M sucrose using a Potter-Elvehjem homogenizer. A crude nuclear pellet was prepared by centrifugation of the homogenate at 1,500xg for 15 min. The crude nuclear pellet was washed two times and resuspended in two volumes of buffer. Glycerol was added to the resuspended pellet to a final concentration of 20%. The enzyme suspension was frozen in aliquots at -80°C. The prostatic and scalp reductases were stable for at least 4 months when stored under these conditions.

5 α -reductase assay.

The reaction mixture contained in a final volume of 100 μ l is: 40 mM buffer (human scalp, potassium phosphate, pH 6.5; human prostatic 5 α -reductase, sodium citrate, pH 5.5), 0.3-10 μ M 14 C-T (or 3 H-T), 1 mM DTT, and 500 μ M NADPH. Typically, the assay was initiated by the addition of 50-100 μ g prostatic homogenate or 75-200 μ g scalp homogenate and incubated at 37°C. After 10-50 min the reaction was quenched by extraction with 250 μ l of a mixture of 70% cyclohexane: 30% ethyl acetate containing 10 μ g each DHT and T. The aqueous and organic layers were separated by centrifugation at 14,000 rpm in an Eppendorf microfuge. The organic layer was subjected to normal phase HPLC (10 cm Whatman partisil 5 silica column equilibrated in 1 ml/min 70 % cyclohexane: 30 % ethyl acetate; retention times DHT, 6.8-7.2 min; androstanediol, 7.6-8.0; T, 9.1-9.7 min). The HPLC system consisted of a Waters Model 680 Gradient System equipped with a Hitachi Model 655A autosampler, Applied Biosystems Model 757 variable UV detector, and a Radiomatic Model A120 radioactivity analyzer. The conversion of T to DHT was monitored using the radioactivity flow detector by mixing the HPLC effluent with one volume of Flo-Scint 1 (Radiomatic). Under the conditions described, the production of DHT was linear for at least 25 min. The only steroids

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observed with the human prostate and scalp preparations were T, DHT and androstenediol.

Stumptail macaque protocol

The following protocol is utilized with the stumptail macaque monkey to demonstrate the effect of compounds of the present invention for promoting hair growth.

Twenty-one male stumptail macaque monkeys of species *Macaca speciosa* are assigned to vehicle control and drug treatment groups on the basis of baseline hair weight data. This assignment procedure is necessary to insure that the average baseline hair growth for each control and experimental group is comparable. The control and drug treatment groups are as follows:

1. Topical 50:30:20 vehicle (N = 6)
2. Oral 5 α -reductase and topical 50:30:20 vehicle (N = 5)
3. Oral placebo (N = 5)
4. 5 α -reductase in vehicle (N = 5)

The vehicle consists of 50% propylene glycol, 30% ethanol and 20% water. A 100 mM concentration of topical 5 α -reductase is formulated in this vehicle. The same 5 α -reductase is administered as an oral dose of 0.5mg per monkey. Immediately prior to the dosing phase of the study, hair is removed from a 1 inch square area (identified by four tatoos) in the center of the balding scalp. This hair collection is the baseline hair growth determination prior to the beginning of treatment.

Approximatly 250 μ L of vehicle and 5 α -reductase in vehicle is prepared and topically administered to the tatoored area of the scelp. The selected 5 α -reductase and placebo is ingested by the monekys at the same time as the topical doses are administered. The monkeys are dosed once per day, seven days per week for twenty weeks.

At four week intervals throughout the dosing phase of the study, each monkey is shaved and the hair is collected and weighed. The body weight data (at baseline and during assay) is analyzed by the

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nonparametric Wilcoxon rank-sum test. Differences are significant at $p < 0.05$. Hair weight data at each week collection for vehicle, placebo and treatment groups are expressed as the change from baseline.

5 Statistical analysis is performed on the rank of the data to show overall differences among groups at each four week collection.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions
10 can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the compounds of the invention indicated above.
15 Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in
20 accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

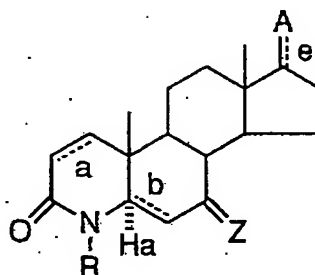
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WHAT IS CLAIMED IS:

1. A compound of the formula:



wherein

R is selected from hydrogen, methyl or ethyl; the dashed lines-a, b, e indicate double bonds which can be present, providing that if b double bond is present, then the 5 α hydrogen, Ha, is not present;

Z can be:

1) oxo,

2) α -hydrogen and a β -substituent selected from C₁-C₄ alkyl, C₂-C₄ alkenyl, -CH₂COOH, hydroxy, carboxy, COOC₁-C₄ alkyl esters; OCONR¹R², where R¹ and R² are independently H, C₁-C₄ alkyl, phenyl, benzyl, and where R¹ and R² together with the nitrogen can form a 5-6 membered saturated heterocyclic ring, optionally with one other heteroatom; OC₁-C₄ alkyl, OC₃-C₆ cycloalkyl, -OCOCH₃, halo, halo C₁-C₂ alkyl, or trifluoromethyl, C₃-C₆ cycloalkyl;

3) =CH-R¹ where R¹ is H, C₁-C₄ alkyl;

4) Spiro



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where R^1 is H, C_1 - C_4 alkyl; and

A can be:

O

IA) -C-Q, where Q is:

(1) NR^2R^3 , where R^3 is independently hydrogen, methyl or ethyl; and R^2 is a hydrocarbon radical, selected from substituted or unsubstituted straight or branched chain alkyl, cycloalkyl, or aralkyl of from 1-12 carbons or monocyclic aryl optionally containing 1 or more lower alkyl substituents of from 1-2 carbon atoms and/or 1 or more halogen substituents, with the proviso that Z is not beta-methyl where R^2 is C_1 - C_8 alkyl;

(2) a hydrocarbon radical being:

(a) a monovalent aliphatic radical selected from straight or branched chain alkyl, or cycloalkyl, of from 1-12 carbons, which can be substituted by one or more of C_1 - C_2 alkyl or halo, excluding C_1 - C_4 alkyl when Z is beta-methyl;

(b) an aralkyl radical selected from benzyl or phenethyl;

(c) a polycyclic aromatic radical which can be substituted with one or more of: -OH, organosilyl protected -OH, -OC $_1$ - C_4 alkyl, C_1 - C_4 alkyl, halo or nitro;

(d) a monocyclic aromatic radical which can be substituted with one or more of:

(i) -OH, -OC $_1$ - C_4 alkyl, C_1 - C_4 alkyl, $-(CH_2)_mOH$, $-(CH_2)_nCOOH$, including organosilyl protected hydroxy, where m is 1-4, n is 1-3, providing C_1 - C_4 alkyl is only present when one of the above oxygen-containing radicals is present;

(ii) -SH, -SC $_1$ - C_4 alkyl, -SOC $_1$ - C_4 alkyl, -SO $_2$ C $_1$ - C_4 alkyl, -SO $_2$ N(C_1 - C_4 -alkyl) $_2$,

- 270 -

-SO₂NH(C₁-C₄alkyl), -(CH₂)_mSH, -S-(CH₂)_n-O-COCH₃, where m is 1-4 n is 1-3, providing C₁-C₄ alkyl is only present when one of the above sulfur containing radicals is present;

(iii) N(R³)₂, which can be protected, where R³ is independently H or C₁-C₄ alkyl, where the monoaryl ring can also be further substituted with C₁-C₄ alkyl; and

(iv) heterocyclic radical selected from 2-, 3-, or 4-pyridyl, 2-pyrrolyl, 2-furyl or thiophenyl; and

(IIA), where:

A is -XR⁴, or -(CHR¹)_n-XR⁴;

n is 1-10;

X is -O- or -S(O)_p-,

wherein p is zero, 1 or 2; and

R¹ can be the same or different when n is greater than 1 and is -H, aryl, or -C₁₋₃alkyl unsubstituted or substituted with C₆-C₁₀ aryl;

R is -H, methyl or ethyl;

R⁴ is 1) hydrogen or -C₁₋₂₀ alkyl, unsubstituted or substituted with one or more of:

a) -OH,

b) halo,

c) -C₁₋₈ alkoxy,

d) -C₁₋₆ alkenyl,

e) -CONR⁵R⁵, wherein R⁵ is independently

i) -H,

ii) -C₁₋₈ alkyl unsubstituted or substituted with one or more of R⁷, aryl or heterocyclic, defined below, the aryl being unsubstituted or substituted one or more of R⁷ or R⁹,

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- iii) aryl unsubstituted or substituted with one or more of R^7 or R^9 , or
iv) heterocyclic, defined below, unsubstituted or substituted with one or more of R^7 or R^9 ,
5 f) $-\text{COOR}^6$, wherein R^6 is
i) $-\text{H}$,
ii) $-\text{C}_{1-8}$ alkyl unsubstituted or substituted with one or more of R^7 or aryl, the aryl being unsubstituted or substituted with one or
10 more of R^7 or R^9 , or
iii) aryl, unsubstituted or substituted with one or more of R^7 or R^9 ,
g) $-\text{S(O)}_p-\text{R}^5$, wherein p is defined above,
h) $-\text{N(R}^5)_2$,
15 i) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9 ,
j) heterocycle, unsubstituted or substituted with one or more of R^7 or R^9 ,
k) $-\text{C}_{3-10}$ cycloalkyl, such as cyclohexyl, norbornyl, or adamantyl, unsubstituted or substituted with one or
20 more of R^7 or R^9 , or
l) $-\text{CONR}^8-\text{CO-NHR}^8$, wherein R^8 is $-\text{H}$, $-\text{C}_{1-8}$ alkyl, benzyl or cyclohexyl; or
25 2) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9 , or
3) heterocycle or $-\text{C}_{3-10}$ cycloalkyl, either of which is unsubstituted or substituted with one or more of R^7 or R^9 ;
30
 R^7 is 1) $-\text{OH}$,
2) $-\text{C}_{1-3}$ alkoxy,
3) $-\text{CN}$,
4) $-\text{COOR}^6$
5) $-\text{C}_{1-8}$ alkyl- COOR^6

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6) $-\text{NO}_2$, or

7) -halo; and

8) amino, mono $\text{C}_1\text{-C}_4$ alkylamino, di $\text{C}_1\text{-C}_4$ alkylamino;

5

R^9 is 1) $-\text{C}_{1-8}$ alkyl, unsubstituted or substituted with one or more of aryl or R^7 ,

2) $-\text{CO-A}$, $-\text{C}_{1-8}$ alkyl- CO-A , $-\text{NHCO-A}$, or $-\text{S(O)}_p\text{-A}$,

wherein p is defined above and A is

10

a) $-\text{H}$,

b) $-\text{C}_{1-8}$ alkyl, unsubstituted or substituted with one or more of

i) $-\text{R}^7$, or

ii) aryl, unsubstituted or substituted with one or more of R^7 , or

15

c) aryl, unsubstituted or substituted with one or more of R^7 ,

3) $-\text{NHCO-heterocycle}$,

4) $-\text{N(R}^{10})_2$ or $-\text{CON(R}^{10})_2$ wherein R^{10} is independently

20

$-\text{H}$, heterocycle, or $-\text{A}$;

5) $-\text{NHCO-(CH}_2)_q\text{-CO-Q}$, wherein q is 1-4, and Q is $-\text{N(R}^{10})_2$ or $-\text{OR}^{10}$;

(III A), where:

25

O

A is $(\text{CHR}^1)_n\text{-X-C-R}^4$;

R^1 can be the same or different when n is greater than 1 and is $-\text{H}$, aryl, or $-\text{C}_{1-3}$ alkyl unsubstituted or substituted with aryl;

30

R is $-\text{H}$, methyl or ethyl;

n is zero through 10;

X is $-\text{O-}$ or $-\text{S-}$; and

R^4 is 1) hydrogen or $-\text{C}_{1-20}$ alkyl, unsubstituted or substituted with one or more of:

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- 5 a) -OH,
b) halo,
c) -C₁₋₈ alkoxy,
d) -C₁₋₆ alkenyl,
e) -CONR⁵R⁵, wherein R⁵ is independently
i) -H,
ii) -C₁₋₈ alkyl unsubstituted or substituted with
one or more of R⁷, aryl or heterocycle, the
10 aryl being unsubstituted or substituted with
one or more of R⁷ or R⁹,
iii) aryl unsubstituted or substituted with one or
more of R⁷ or R⁹, or
iv) heterocycle, unsubstituted or substituted with
one or more of R⁷ or R⁹,
15 f) -COOR⁶, wherein R⁶ is
i) -H,
ii) -C₁₋₈ alkyl unsubstituted or substituted with
one or more of R⁷ or aryl, the aryl being
unsubstituted or substituted with one or
20 more of R⁷ or R⁹, or
iii) aryl, unsubstituted or substituted with one or
more of R⁷ or R⁹,
g) -S(O)_p-R⁵, wherein p is zero, 1 or 2;
h) -N(R⁵)₂,
25 i) aryl, unsubstituted or substituted with one or
more of aryl, R⁷ or R⁹,
j) heterocycle, unsubstituted or substituted with one or
more of R⁷ or R⁹,
30 k) -C₃₋₁₀ cycloalkyl, such as cyclohexyl, norbornyl, or
adamantyl, unsubstituted or substituted with one
or more of R⁷ or R⁹, or
l) -CONR⁸-CO-NHR⁸, wherein R⁸ is -H, -C₁₋₈ alkyl, benzyl
or cyclohexyl,

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- 2) aryl, unsubstituted or substituted with one or more of aryl,
 R^7 or R^9 ,
 3) heterocycle or $-C_{3-10}$ cycloalkyl, either of which is
 unsubstituted or substituted with one or more of R^7 or
 R^9 ,
 4) $-NR^5R^5$, or
 5) $-OR^5$;

R^7 is 1) $-OH$,

2) $-C_{1-3}$ alkoxy,

3) $-CN$,

4) $-COOR^6$

5) $-C_{1-8}$ alkyl- $COOR^6$

6) $-NO_2$, or

7) halo; and

8) amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino;

R^9 is 1) $-C_{1-8}$ alkyl, unsubstituted or substituted with one or more
 of aryl or R^7 ,

2) $-CO-A$, $-C_{1-8}$ alkyl- $CO-A$, $-NHCO-A$, or $-S(O)_p-A$,

wherein p is defined above and A is

a) $-H$,

b) $-C_{1-8}$ alkyl, unsubstituted or substituted with one or
 more of

i) $-R^7$, or

ii) aryl, unsubstituted or substituted with one or
 more of R^7 , or

c) aryl, unsubstituted or substituted with one or more of
 R^7 ,

3) $-NHCO$ -heterocycle,

4) $-N(R^{10})_2$ or $-CON(R^{10})_2$ wherein R^{10} is independently,
 heterocycle or $-A$,

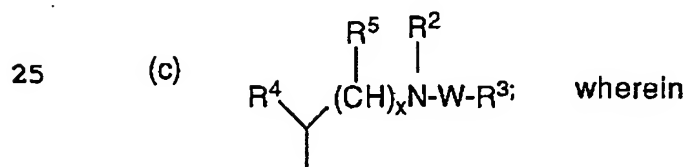
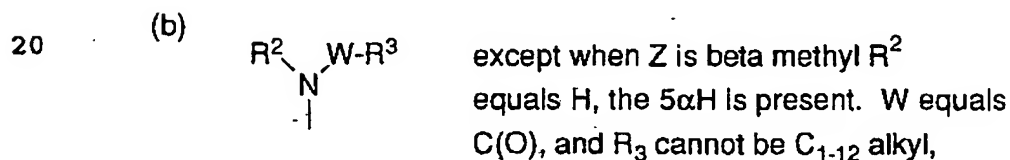
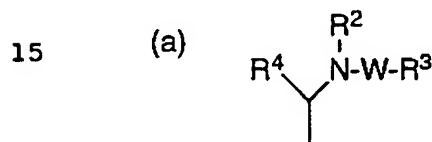
5) $-NHCO-(CH_2)_q-CO-Q$, wherein q is 1-4, and Q is $-N(R^{10})_2$
 or $-OR^{10}$;

- 275 -

with the provisos that when Z is beta-methyl, the following are excluded:

- 5 when n is 1-12, R¹ is -H at each occurrence, X is -O-, and R⁴ is -C₁₋₆alkyl, R⁴ is not substituted with an unsubstituted phenyl ring;
- when n is 1-12, R¹ is -H at each occurrence, and X is -O-, R⁴ is not unsubstituted C₅₋₁₀cycloalkyl, unsubstituted phenyl, amino, -C₁₋₈alkyl substituted amino, or -C₁₋₈alkoxy; and
- 10 when n is zero, R⁴ is not -CH₃; and

(IVA), where A is:



30 R² is:
H, methyl or ethyl;

R³ is:
H,
mono C₁-C₄ alkylaminoaryl,

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- di C₁-C₄ alkylaminoaryl,
C₁-20 alkyl,
C₆-C₁₄ aryl,
heteroaryl, as defined below,
5 C₆-C₁₄ arylC₁-20alkyl,
heteroarylC₁-20alkyl,
C₁-20alkylthioC₁-20alkyl,
C₁-20alkylsulfinylC₁-20alkyl,
C₁-20alkylsulfonylC₁-20alkyl,
10 C₁-20alkyloxycarbonylC₁-20alkyl,
carboxylC₁-20alkyl,
C₁-20 alkylcarbonylC₁-20alkyl,
C₃-20cycloalkyl,
C₃-20cycloalkylC₁-20alkyl,
15 C₆-C₁₄ arylC₁-20alkyloxycarbonylC₁-20alkyl,
heteroarylC₁-20alkyloxycarbonylC₁-20alkyl,
haloC₁-20alkyl,
hydroxylC₁-20alkyl,
thiosulfatoC₁-20alkyl,
20 C₆-C₁₄ arylC₁-20alkyloxyC₁-20alkyl,
C₁-20alkyloxyC₁-20alkyl,
arylcarbonylarylC₁-20alkyl,
diarylC₁-20alkyl,
triarylC₁-20alkyl,
25 C₂-20 alkenyl,
C₂-20 alkenylC₁-20alkyl,
heteroarylC₂-20alkenyl,
arylC₂-20alkenyl,
C₂-20alkynylC₁-20alkyl,
30 arylC₂-20alkynylC₁-20alkyl, or
heteroarylC₂-20alkynylC₁-20alkyl;

R⁴ is:

H,

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C₁₋₂₀ alkyl,
C₆₋₁₄ aryl or
heteroaryl;

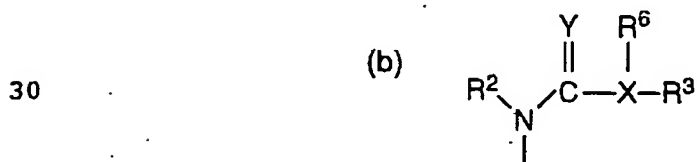
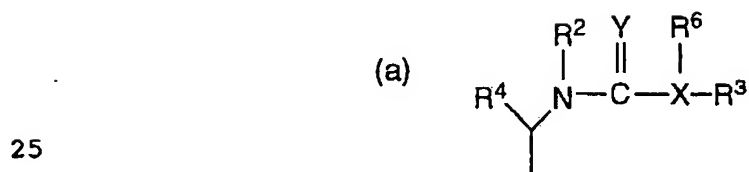
5 R⁵ can be the same or different when X is greater
than 1 and is:
H, or
C₁₋₂₀ alkyl;

10 W is:

O
- C -, or
O
15 - S -,
O

x is an integer from 1-25;

20 (VA), where:
A is:



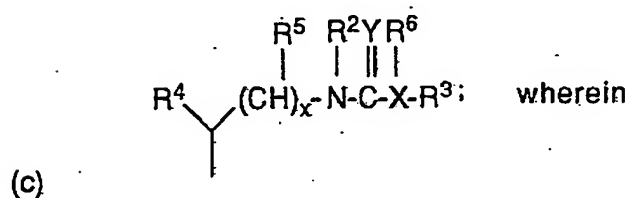
except when Z is beta methyl, R² equals H, Y equals
O, X equals N and the 5αH is present, R⁶ and R³

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can not be independently selected from H, C₁₋₈
alkyl, C₃₋₆ cycloalkyl, phenyl and R⁶ and R³
cannot be taken together with the adjacent N to
form a 5-6 membered ring comprising up to one
other heteroatom selected from O or N, or

5

10

15 R² is:

H, or
C₁₋₂₀ alkyl;

20 R³ is:

H,
amino,
mono C₁₋₄ alkylamino,
di C₁₋₄ alkylamino,
mono C₁₋₄ alkylaminoaryl,
di C₁₋₄ alkylaminoaryl,
C₁₋₂₀ alkyl,
C₆₋₁₄ aryl,
heteroaryl,
C₆₋₁₄ arylC₀₋₂₀alkyl,
C₃₋₂₀ cycloalkyl,
C₃₋₂₀ cycloalkylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyl,
C₂₋₂₀ alkenylC₁₋₂₀alkyl,
haloC₁₋₂₀alkyl,
C₁₋₂₀alkyloxycarbonyl,

25

30

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C₁-20alkyl,
C₁-20 alkyloxyC₁-20alkyl,
carboxyC₁-20alkyl,
5 C₆-C₁₄arylcarbonylarylC₁-20alkyl,
C₁-20 alkylcarbonylC₁-20alkyl,
C₆-C₁₄arylC₁-20alkyloxy carbonylC₁-20alkyl,
heteroarylC₁-20alkyloxy carbonylC₁-20alkyl,
hydroxylC₁-20alkyl,
10 halohydroxylC₁-20alkyl,
arylC₁-20alkyloxyC₁-20alkyl,
heteroarylC₁-20alkyloxyC₁-20alkyl,
diarylC₁-20alkyl,
triarylC₁-20alkyl,
15 C₂-20 alkenyl,
C₂-20 alkenylC₁-20alkyl,
C₂-20 alkynylC₁-20alkyl,
arylC₂-20alkynylC₁-20alkyl,
heteroarylC₂-20alkynylC₁-20alkyl,
20 C₁-20 alkylthioC₁-20alkyl,
C₁-20 alkylsulfonylC₁-20alkyl, or
C₁-20 alkylsulfinyl C₁-20alkyl;

R⁴ is:

25 H,
C₁-20 alkyl,
heteroaryl, or
C₆-C₁₄ aryl;

30 R⁵ can be the same or different when X is greater
than 1 and is:
H,
C₁-20 alkyl,
heteroaryl, or
C₆-C₁₄ aryl;

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R^6 is present when X equals N and is independently

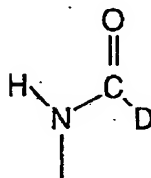
H,

or C_1 - C_{20} alkyl and can be taken together with R^3 and the N

to which they are attached to form a heteroaryl ring system; as defined below, and

(VIA), where:

A is(a)



D is R^1 or OR^1 ,

where R^1 is: C_1 - C_{10} alkyl,

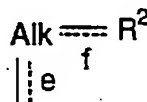
C_3 - C_{12} cycloalkyl,

C_6 - C_{10} aryl, or

C_7 - C_{11} aralkyl with the proviso that when D is R^1 and Z is beta-methyl, the value of C_1 - C_{10} alkyl is excluded; and

(b) $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{OC}_1-\text{C}_{12} \text{ alkyl} \end{array}$, providing Z is not methyl;

(VIIA), where A is of the formula:



wherein:

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Alk is C₁-C₄ straight or branched chain alkyl or alkenyl; dashed lines e and f each can independently represent a double bond when present, with the proviso that double bonds formed by e and f are not both present concurrently; and

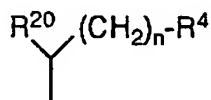
R² is (a) C₆-C₁₀ aryl, or 5-6 membered heteroaryl radical which can contain 1-4 nitrogen atoms, one oxygen or sulfur atoms or combinations thereof with 1-2 nitrogen atoms;

(b) COR₁, where R₁ is C₆-C₁₀ aryl, substituted C₆-C₁₀ aryl, and heteroaryl;

(c) CONHR₂, where R₂ is substituted phenyl, heteroaryl, substituted heteroaryl, or C₇ to C₁₂ cycloalkyl;

(d) CO₂R₃, where R₃ is C₁-C₁₈ linear or branched alkyl, C₆-C₁₀ aryl, substituted C₆-C₁₀ aryl, or C₇-C₁₂ cycloalkyl; providing that in (b), (c) or (d), Alk is only alkenyl;

(VIII A), where A is of the structure:



where:

R²⁰ is H, methyl;

n is 0-10

R⁴ is selected from:

(a) -COR¹, where R¹ is phenyl or substituted phenyl;

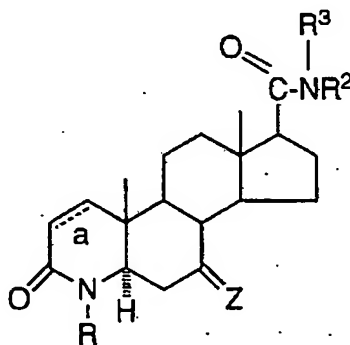
(b) -CONHR², where R² is substituted phenyl, heteroaryl, substituted heteroaryl;

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(c)-COOR³, where R³ is phenyl, substituted phenyl, heteroaryl, substituted heteroaryl;

5 wherein said heteroaryl radical is a 5-6 membered ring which can contain 1-4 nitrogen atoms, one oxygen or sulfur atom, or combinations thereof with 1-2 nitrogen atoms, and wherein phenyl and heteroaryl can be substituted; wherein the above aryl or heteroaryl radicals can also
10 be fused with a benzo or another heteroaryl ring and can further be substituted with one or more substituents; and stereoisomers and pharmaceutically acceptable salts and esters thereof.

15 2. The compound of Claim 1 of the formula:



25

wherein:

Z is as defined above;

the dotted line a represents a double bond when present;

30 R and R³ are independently hydrogen, methyl or ethyl; R² is a hydrocarbon radical, selected from substituted or unsubstituted straight or branched chain alkyl, cycloalkyl, or aralkyl of from 1-12 carbons or monocyclic aryl optionally 1 or more lower alkyl substituents of from 1-2 carbon atoms and/or 1 or more halogen substituents.

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3. The compound according to Claim 2 wherein: the dotted line is a double bond;

R is hydrogen or methyl; R^3 is hydrogen;

5 R^2 is branched chain alkyl, cycloalkyl, aralkyl, or from 4-12 carbon atoms, or phenyl, optionally substituted by methyl, chloro or fluoro.

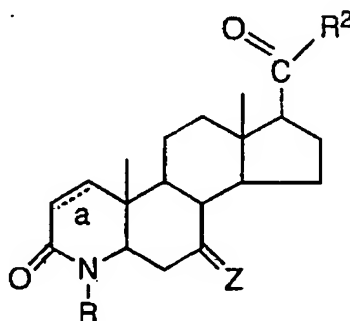
4. The compound of Claim 2 wherein the dotted line is
10 a double bond and R^2 is a substituted or unsubstituted 1-, 2-adamantyl, 1-, 2-adamantylmethyl, 1-, 2- or 7-norbornanyl, 1-, 2- or 7-norbornanylmethyl.

5. The compound of Claim 4 wherein the 1- or 2-adamantyl or 1- or 2-norbornanyl moieties can be substituted with
15 one or more of: C_1 - C_4 linear or branched alkyl, nitro, oxo, C_7 - C_9 aralkyl, $(CH_2)_n$ COOR where n is 0-2 and R is H or linear/branched C_1 - C_4 alkyl, CH_2OH , OH, OR where R is C_1 - C_4 linear/branched alkyl, halo, $CONH_2$, CH_2NH_2 , CH_2NHCOR where R is C_1 - C_4
20 linear/branched alkyl, phenyl, p-nitrophenyl, p-aminophenyl, p-sulfophenyl or cyano.

6. The compound of Claim 1 of the formula:

25

30



wherein: Z is as defined above; the dotted line a represents a double bond when present and,

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R is selected from hydrogen, methyl and ethyl; and

R² is (a) a monovalent radical selected from straight or branched chain alkyl, or cycloalkyl, or from 1-12 carbons, which can be substituted by one or more of C₁-C₂ alkyl or halo;

(b) an aralkyl radical selected from benzyl or phenethyl;

(c) a polycyclic aromatic radical which can be substituted with one or more of: -OH, organosilyl protected -OH, -OC₁-C₄ alkyl, C₁-C₄ alkyl, halo or nitro;

(d) a monocyclic aromatic radical which can be substituted with one or more of:

(1) -OH, -OC₁-C₄ alkyl, C₁-C₄ alkyl, -(CH₂)_mOH, -(CH₂)_n, COOH, including organosilyl protected hydroxy, where m is 1-4, n is 1-3, providing C₁-C₄ alkyl is only present when one of the above oxygen-containing radicals is present;

(2) -SH, -SC₁-C₄ alkyl, -SOC₁-C₄ alkyl, -SO₂C₁-C₄ alkyl, -SO₂N(C₁-C₄-alkyl)₂, C₁-C₄ alkyl -(CH₂)_mSH, -S-(CH₂)_n-O-COCH₃, where m is 1-4 n is 1-3, providing C₁-C₄ alkyl is only present when one of the above sulfur containing radicals is present;

(3) N(R³)₂, which can be protected, where R³ is independently H or C₁-C₄ alkyl, where the monoaryl ring can be also be further substituted with C₁-C₄ alkyl; and

(e) heterocyclic radical selected from 2- or 4-pyridyl, 2-pyrrolyl, 2-furyl or thiophenyl.

7. The compound of Claim 6

wherein the dotted line is a double bond,
R is hydrogen or methyl; and

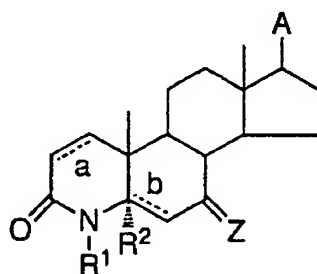
- 285 -

R^2 is phenyl, 2-, 3-, or 4-tolyl, xylyl, 2-bromophenyl, 2-chlorophenyl, 2,6-dichlorophenyl, 2,6-dibromophenyl, aminophenyl, N-alkylaminophenyl, N-N-dialkylaminophenyl, 4-biphenyl, 3-biphenyl, naphthyl, anthracyl, phenanthryl, thiophenyl, methylthiophenyl, methylsulfinyl, phenyl, methylsulfonyl, aminosulfonyl, thioethylphenyl, acetoxymethylthiophenyl, 17 β -(4-hydroxyphenyl), 17 β -(3-hydroxyphenyl), 17 β -(3,4-dihydroxyphenyl), or 17 β -(3,5-dimethyl-4-hydroxyphenyl).

8. The compound of Claim 1 of the formula

15

20



wherein: Z is defined in Claim 1;
 wherein a and b are both single bonds and R^2 is hydrogen, or
 a is a double bond, b is a single bond and R^2 is hydrogen, or
 a is a single bond, b is a double bond and R^2 is absent;
 A is $-XR^4$, or $-(CHR^1)_n-XR^4$;
 n is 1-10;
 X is $-O-$ or $-S(O)_p-$,
 wherein p is zero, 1 or 2; and
 R^1 as defined above is $-H$, aryl, or $-C_{1-3}$ alkyl unsubstituted or
 substituted with aryl;
 R^1 is $-H$, methyl or ethyl;

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R⁴ is 1) -C₁₋₂₀ alkyl, unsubstituted or substituted with one or more of:

- 5
- a) -OH,
 - b) halo,
 - c) -C₁₋₈ alkoxy,
 - d) -C₁₋₆ alkenyl,
 - e) -CONR⁵R⁵, wherein R⁵ is independently
 - 10 i) -H,
 - ii) -C₁₋₈ alkyl unsubstituted or substituted with one or more of R⁷, aryl or heterocycle, the aryl being unsubstituted or substituted with one or more of R⁷ or R⁹,
 - 15 iii) aryl unsubstituted or substituted with one or more of R⁷ or R⁹, or
 - iv) heterocycle, unsubstituted or substituted with one or more of R⁷ or R⁹,
 - f) -COOR⁶, wherein R⁶ is
 - 20 i) -H,
 - ii) -C₁₋₈ alkyl unsubstituted or substituted with one or more of R⁷ or aryl, the aryl being unsubstituted or substituted with one or more of R⁷ or R⁹,
or
 - 25 iii) aryl, unsubstituted or substituted with one or more of R⁷ or R⁹,
 - g) -S(O)_p-R⁵, wherein p is defined above,
 - h) -N(R⁵)₂,
 - 30 i) aryl, unsubstituted or substituted with one or more of aryl, R⁷ or R⁹,
 - j) heterocycle, unsubstituted or substituted with one or more of R⁷ or R⁹,
 - k) -C₃₋₁₀ cycloalkyl, such as cyclohexyl, norbornyl, or adamantyl, unsubstituted or substituted with one or more of R⁷ or R⁹, or

- 287 -

- 1) $-\text{CONR}^8-\text{CO}-\text{NHR}^8$, wherein R^8 is $-\text{H}$, $-\text{C}_{1-8}$ alkyl, benzyl or cyclohexyl; or
- 2) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9 , or
- 3) heterocycle or $-\text{C}_{3-10}$ cycloalkyl, either of which is unsubstituted or substituted with one or more of R^7 or R^9 ;

- R^7 is 1) $-\text{OH}$,
2) $-\text{C}_{1-3}$ alkoxy,
3) $-\text{CN}$,
4) $-\text{COOR}^6$
5) $-\text{C}_{1-8}$ alkyl- COOR^6
6) $-\text{NO}_2$, or
7) $-\text{halo}$; and
8) amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino;

- R^9 is 1) $-\text{C}_{1-8}$ alkyl, unsubstituted or substituted with one or more of aryl or R^7 ,
2) $-\text{CO}-\text{A}$, $-\text{C}_{1-8}$ alkyl- $\text{CO}-\text{A}$, $-\text{NHCO}-\text{A}$, or $-\text{S}(\text{O})_p-\text{A}$, wherein p is defined above and A is
a) $-\text{H}$,
b) $-\text{C}_{1-8}$ alkyl, unsubstituted or substituted with one or more of
i) $-\text{R}^7$, or
ii) aryl, unsubstituted or substituted with one or more of R^7 , or
c) aryl, unsubstituted or substituted with one or more of R^7 ,
3) $-\text{NHCO}$ -heterocycle,
4) $-\text{N}(\text{R}^{10})_2$ or $-\text{CON}(\text{R}^{10})_2$ wherein R^{10} is independently $-\text{H}$, heterocycle, or $-\text{A}$,

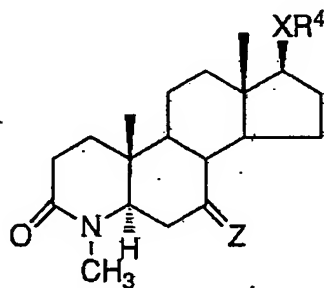
- 288 -

5) $\text{-NHCO-(CH}_2\text{)}_q\text{-CO-Q}$, wherein q is 1-4, and Q is $\text{-N(R}^{10}\text{)}_2$ or -OR^{10} .

5

9. The compound of Claim 8 having structural formula:

10



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10. The compound of Claim 9 wherein R^4 is -C_{1-20} alkyl, unsubstituted or substituted with one or more of -OH , halo, -C_{1-8} alkoxy, -C_{1-6} alkenyl, $\text{-S(O)}_p\text{-R}^5$, $\text{-N(R}^5\text{)}_2$, aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9 , heterocycle unsubstituted or substituted with one or more of R^7 or R^9 , or -C_{3-10} cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9 .

20

25

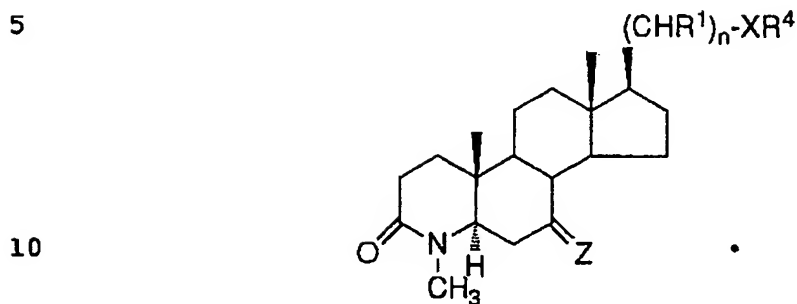
11. The compound of Claim 9 wherein R^4 is -C_{1-20} alkyl substituted with $\text{-CONR}^5\text{R}^5$, -COOR^6 or $\text{-CONR}^8\text{CONHR}^8$.

30

12. The compound of Claim 9 wherein R^4 is aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9 ; heterocycle unsubstituted or substituted with one or more of R^7 or R^9 ; or -C_{3-10} cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9 .

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13. The compound of Claim 8 having structural formula:



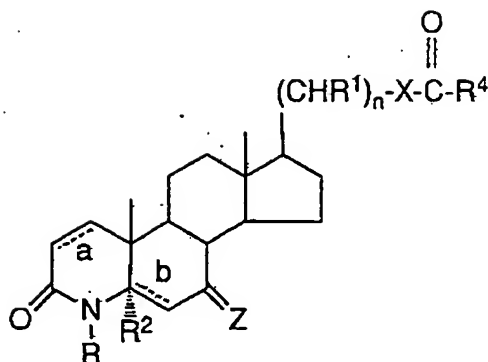
14. The compound of Claim 13 wherein R^4 is $-C_{1-20}$ alkyl, unsubstituted or substituted with one or more of $-OH$, halo, $-C_{1-6}$ alkoxy, $-C_{1-6}$ alkenyl, $-S(O)_p-R^5$, $-N(R^5)_2$, aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9 , heterocycle unsubstituted or substituted with one or more of R^7 or R^9 , or $-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9 .

15. The compound of Claim 13 wherein R^4 is $-C_{1-20}$ alkyl substituted with $-CONR^5R^5$, $-COOR^6$ or $-CONR^8CONHR^8$.

16. The compound of Claim 13 wherein R^4 is aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9 ; heterocycle unsubstituted or substituted with one or more of R^7 or R^9 ; or $-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9 .

17. A compound of Claim 1 of the formula:

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wherein: Z is as defined above;

a and b are both single bonds and R² is hydrogen, or a is a double bond, b is a single bond and R² is hydrogen, or a is a single bond, b is a double bond and R² is absent;

R¹ can be the same or different when n is greater than 1 and is -H, aryl, or -C₁₋₃alkyl unsubstituted or substituted with aryl;

R is -H, methyl or ethyl;

n is zero through 10;

X is -O- or -S-; and

R⁴ is 1) -C₁₋₂₀ alkyl, unsubstituted or substituted with one or more of:

a) -OH,

b) halo,

c) -C₁₋₈ alkoxy,

d) -C₁₋₆ alkenyl,

e) -CONR⁵R⁵, wherein R⁵ is independently

i) -H,

ii) -C₁₋₈ alkyl unsubstituted or substituted with one or more of R⁷, aryl or heterocycle, the aryl being unsubstituted or substituted with one or more of R⁷ or R⁹,

iii) aryl unsubstituted or substituted with one or more of R⁷ or R⁹, or

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- iv) heterocycle, unsubstituted or substituted with one or more of R^7 or R^9 ,
- f) $-\text{COOR}^6$, wherein R^6 is
- 5 i) $-\text{H}$,
- ii) $-\text{C}_{1-8}$ alkyl unsubstituted or substituted with one or more of R^7 or aryl, the aryl being unsubstituted or substituted with one or more of R^7 or R^9 , or
- 10 iii) aryl, unsubstituted or substituted with one or more of R^7 or R^9 ,
- g) $-\text{S(O)}_p-\text{R}^5$, wherein p is zero, 1 or 2;
- h) $-\text{N(R}^5)_2$,
- i) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9 ,
- 15 j) heterocycle, unsubstituted or substituted with one or more of R^7 or R^9 ,
- k) $-\text{C}_{3-10}$ cycloalkyl, such as cyclohexyl, norbornyl, or adamantyl, unsubstituted or substituted with one or more of R^7 or R^9 , or
- 20 l) $-\text{CONR}^8-\text{CO-NHR}^8$, wherein R^8 is $-\text{H}$, $-\text{C}_{1-8}$ alkyl, benzyl or cyclohexyl,
- 2) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9 ,
- 25 3) heterocycle or $-\text{C}_{3-10}$ cycloalkyl, either of which is unsubstituted or substituted with one or more of R^7 or R^9 ,
- 4) $-\text{NR}^5\text{R}^5$, or
- 5) $-\text{OR}^5$;
- 30 R^7 is 1) $-\text{OH}$,
- 2) $-\text{C}_{1-3}$ alkoxy,
- 3) $-\text{CN}$,
- 4) $-\text{COOR}^6$
- 5) $-\text{C}_{1-8}$ alkyl- COOR^6

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6) $-\text{NO}_2$, or

7) halo; and

8) amino, mono $\text{C}_1\text{-C}_4$ alkylamino, di $\text{C}_1\text{-C}_4$ alkylamino;

5 R^9 is 1) $-\text{C}_{1-8}$ alkyl, unsubstituted or substituted with one or more of aryl or R^7 ,

2) $-\text{CO-A}$, $-\text{C}_{1-8}$ alkyl- CO-A , $-\text{NHCO-A}$, or $-\text{S(O)}_p\text{-A}$,

wherein p is defined above and A is

a) $-\text{H}$,

10 b) $-\text{C}_{1-8}$ alkyl, unsubstituted or substituted with one or more of

i) $-\text{R}^7$, orii) aryl, unsubstituted or substituted with one or more of R^7 , or

15 c) aryl, unsubstituted or substituted with one or more of R^7 ,

3) $-\text{NHCO-heterocycle}$,4) $-\text{N(R}^{10})_2$ or $-\text{CON(R}^{10})_2$ wherein R^{10} is independently, heterocycle or $-\text{A}$,

20 5) $-\text{NHCO-(CH}_2)_q\text{-CO-Q}$, wherein q is 1-4, and Q is $-\text{N(R}^{10})_2$ or $-\text{OR}^{10}$;

with the provisos that when Z is beta methyl, the following are excluded:

25 when n is 1-10, R^1 is $-\text{H}$ at each occurrence, X is $-\text{O-}$, and R^4 is $-\text{C}_{1-6}$ alkyl, R^4 is not substituted with an unsubstituted phenyl ring;

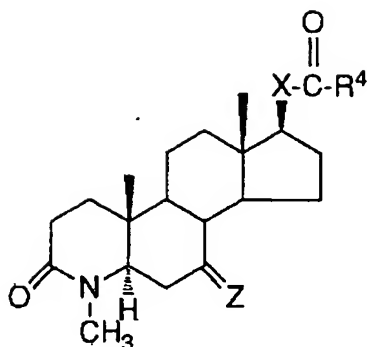
30 when n is 1-10, R^1 is $-\text{H}$ at each occurrence, and X is $-\text{O-}$, R^4 is not unsubstituted C_{5-10} cycloalkyl, unsubstituted phenyl, amino, $-\text{C}_{1-8}$ alkyl substituted amino, or $-\text{C}_{1-8}$ alkoxy; and

when n is zero, R^4 is not $-\text{CH}_3$.

18. The compound of Claim 17 having structural formula:

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19. The compound of Claim 18 wherein R^4 is $-C_{1-20}$ alkyl, unsubstituted or substituted with one or more of $-OH$, halo, $-C_{1-8}$ alkoxy, $-C_{1-6}$ alkenyl, $-S(O)_p-R^5$, $-N(R^5)_2$, aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9 , heterocycle unsubstituted or substituted with one or more of R^7 or R^9 , or $-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9 .

20

20. The compound of Claim 18 wherein R^4 is $-C_{1-20}$ alkyl substituted with $-CONR^5R^5$, $-COOR^6$ or $-CONR^8CONHR^8$.

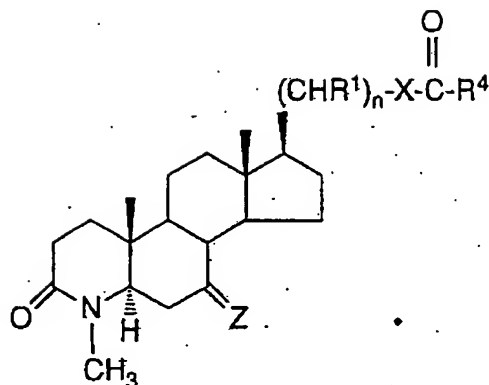
25

21. The compound of Claim 18 wherein R^4 is aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9 ; heterocycle unsubstituted or substituted with one or more of R^7 or R^9 ; $-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9 ; $-NR^5R^5$; or $-OR^5$.

30

22. The compound of Claim 17 having structural formula:

- 294 -



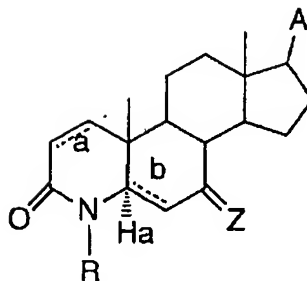
23. The compound of Claim 22 wherein R^4 is -C_{1-20} alkyl, unsubstituted or substituted with one or more of -OH , halo, -C_{1-6} alkoxy, -C_{1-6} alkenyl, $\text{-S(O)}_p\text{-R}^5$, $\text{-N(R}^5)_2$, aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9 , heterocycle unsubstituted or substituted with one or more of R^7 or R^9 , or -C_{3-10} cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9 .

24. The compound of Claim 22 wherein R^4 is -C_{1-20} alkyl substituted with $\text{-CONR}^5\text{R}^5$, -COOR^6 or $\text{-CONR}^8\text{CONHR}^8$.

25. The compound of Claim 22 wherein R^4 is aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9 ; heterocycle unsubstituted or substituted with one or more of R^7 or R^9 ; -C_{3-10} cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9 ; $\text{-NR}^5\text{R}^5$; or -OR^5 .

26. The compound of Claim 1 of the formula:

- 295 -

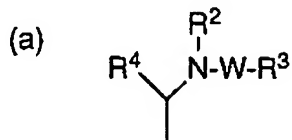


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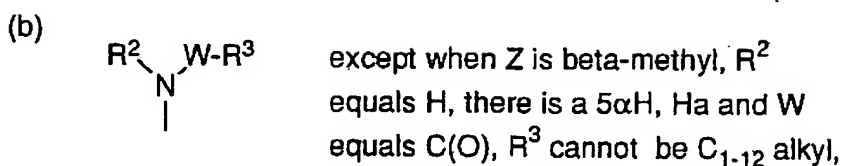
wherein:
 10 Z is as defined above;

A is:

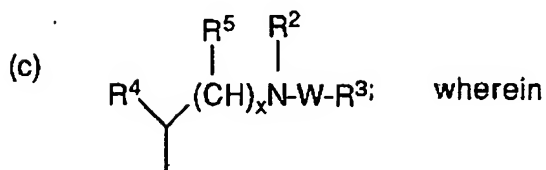
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20



25



30 R² is:
 H,
 C₁₋₂₀ alkyl;

R³ is:
 H,

- 296 -

mono-C₁-C₄ alkylaminoaryl,
di C₁-C₄ alkylaminoaryl,
C₁-20 alkyl,
C₆₋₁₄ aryl,
5 heteroaryl, as defined above,
C₆₋₁₄ arylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyl,
C₁₋₂₀alkylthioC₁₋₂₀alkyl,
C₁₋₂₀alkylsulfinylC₁₋₂₀alkyl,
10 C₁₋₂₀alkylsulfonylC₁₋₂₀alkyl,
C₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
carboxylC₁₋₂₀alkyl,
C₁₋₂₀alkylcarbonylC₁₋₂₀alkyl,
C₃₋₂₀cycloalkyl,
15 C₃₋₂₀cycloalkylC₁₋₂₀alkyl,
C₆₋₁₄ arylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl;
haloC₁₋₂₀alkyl,
hydroxylC₁₋₂₀alkyl,
20 halohydroxylC₁₋₂₀alkyl,
thiosulfatoC₁₋₂₀alkyl,
C₆₋₁₄ arylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
C₁₋₂₀alkyloxyC₁₋₂₀alkyl,
C₆₋₁₄ arylcarbonylC₅₋₁₄arylC₁₋₂₀alkyl,
25 diarylC₁₋₂₀alkyl,
triarylC₁₋₂₀alkyl,
C₂₋₂₀ alkenyl,
C₂₋₂₀ alkenylC₁₋₂₀alkyl,
heteroarylC₂₋₂₀alkenyl,
30 C₆₋₁₄ arylC₂₋₂₀alkenyl,
C₂₋₂₀alkynylC₁₋₂₀alkyl,
C₆₋₁₄ arylC₂₋₂₀alkynylC₁₋₂₀alkyl, or
heteroarylC₂₋₂₀alkynylC₁₋₂₀alkyl;

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R⁴ is:

5 H,
 C₁₋₂₀ alkyl,
 C₆₋₁₄ aryl or
 heteroaryl;

R⁵ can be the same or different when X is greater
than 1 and is:

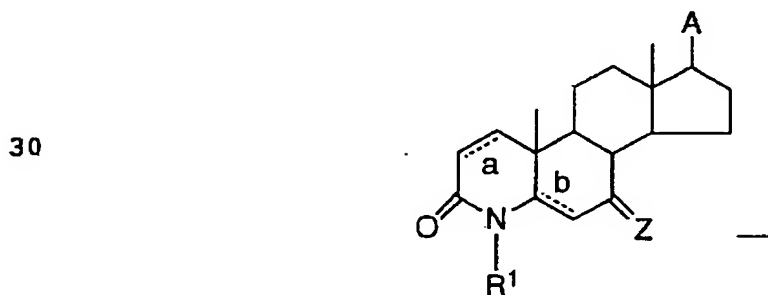
10 H, or
 C₁₋₁₂ alkyl;

W is:

15 O
 - C -, or
 O
 - S -,
 O

20 x is an integer from 1-25;
 and the dashes a and b indicate double bonds which can be optionally
 present.

25 27. A compound according to Claim 26 of the
 formula:

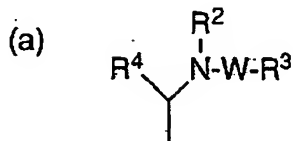


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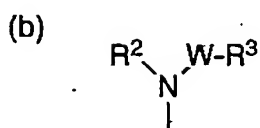
wherein: Z is defined in Claim 1:

A is:

5

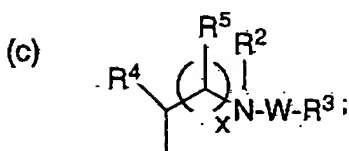


10



except when Z equals β -methyl and equals H, there is a 5α H and W equals C(O), R^3 cannot be C_{1-12} alkyl,

15



wherein

20

R^2 is:

H, or
 C_{1-20} alkyl;

25

R^3 is:

H,
 C_{1-20} alkyl further comprising a straight or branched chain
alkane of up to 20 carbon atoms;

30

C_{6-14} aryl wherein aryl comprises a mono or polycyclic
system composed of 6-membered aromatic rings either
unsubstituted or substituted with R wherein R comprises
H, C_{1-6} alkyl, aryl C_{1-20} alkyl with the alkyl groups
unsubstituted or substituted with hydroxyl, C_{1-}

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galkyloxy, carboxy C₀₋₁₀alkyl, or halogen or aryl is directly substituted independently with hydroxyl, haloC₁₋₂₀alkyl, carboamide, benzoyl, C₁₋₂₀alkyloxy, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, cyano, nitro, acetamide or halogen;

heteroaryl which comprises a mono or polycyclic system composed of 5 or 6-membered aromatic rings containing 1, 2, 3 or 4 heteroatoms chosen from N, O, or S and either unsubstituted or substituted with R or independently with hydroxyl C₁₋₂₀alkyloxy, C₁₋₂₀alkyl, benzoyl, carboxamide, acetamide, halogens, C₂₋₂₀alkenyl, cyano, nitro, or haloalkyl directly bonded to the aromatic carbon atom(s);

C₆₋₁₄ arylC₁₋₂₀alkyl of the formula:



wherein the aromatic ring is optionally and independently substituted with R⁷ and R⁸ wherein R⁷ and R⁸ comprise:

25 H,
CH₃,
C₂H₅,
carboxamido,
C₁-C₆ alkylthio,
30 C₁-C₆ alkylsulfinyl,
C₁-C₆ alkylsulfonyl,
OCH₃,
NH₂,
CH₃NH₂

- 300 -

(CH₃)₂N,

OH,

NO₂,

CN,

F,

acetamido,

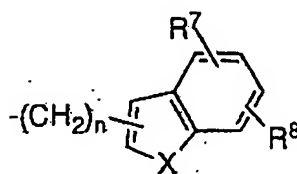
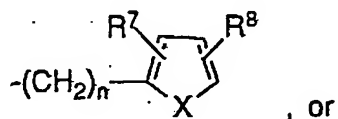
Cl,

OC₂H₅,CF₃,

isopropyl, or

isobutyl; n equals 1-20 and the C₁-20alkyl portion is optionally substituted with R⁷;

HeteroarylC₁-20alkyl further comprising the formula



wherein X equals O, S, or NR; and n equals 1-20;

C₁-20alkylsulfonylC₁-20alkyl

C₁-20alkylthioC₁-20alkyl

C₁-20alkylsulfinylC₁-20alkyl comprising the formula:

-(CH₂)_nS(O)_p-R⁹ wherein R⁹ comprises

CH₃,

C₂H₅,

- 301 -

n-C₃H₇,
 n-C₄H₉,
 isopropyl,
 isobutyl,
 5 sec-butyl,
 t-butyl,
 isopentyl,
 neopentyl, or
 10 isohexyl; n equals 1-15; p equals 0-2;

C₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl further comprising the formula:

15
$$-(\text{CH}_2)_n-\overset{\text{O}}{\underset{|}{\text{C}}}-\text{OR}^{10}$$
 wherein R¹⁰
 comprises:
 CH₃,
 C₂H₅, linear or branched;
 C₃H₇,
 20 C₄H₉, or
 C₅H₁₁; and n equals 1-20;

CarboxylC₁₋₂₀alkyl further comprising:

25
$$-(\text{CH}_2)_n-\overset{\text{O}}{\underset{|}{\text{C}}}-\text{OH}; n = 1-20;$$

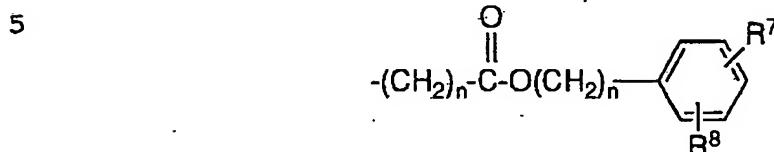
C₁₋₂₀alkylcarbonylC₁₋₂₀alkyl further comprising the formula

30
$$-(\text{CH}_2)_n-\overset{\text{O}}{\underset{|}{\text{C}}}(\text{CH}_2)_m-\text{CH}_3, n \text{ equals } 1-20; m \text{ equals } 0-19;$$

C₃₋₂₀cycloalkylC₁₋₂₀alkyl of the formula: $-(\text{CH}_2)_n-$
 (cycloalkyl) wherein the cycloalkyl portion comprises
 monocyclic, bicyclic, or polycyclic hydrocarbons of up
 to 20 carbon atoms wherein the rings are optionally
 substituted with R¹; and n = 1-20;

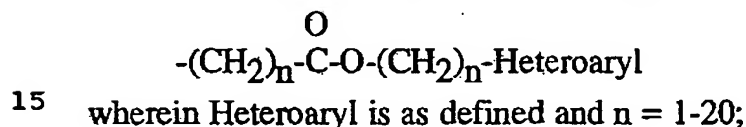
- 302 -

ArylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl of the formula:

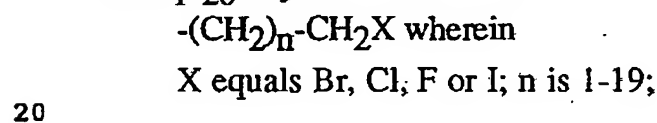


10 wherein n = 1-20;

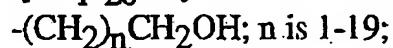
HeteroarylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl of the formula:



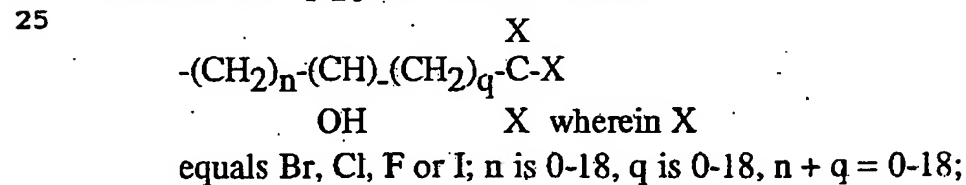
haloC₁₋₂₀alkyl of the formula:



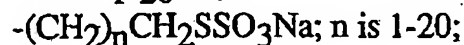
hydroxylC₁₋₂₀alkyl of the formula:



halohydroxylC₁₋₂₀alkyl of the formula:

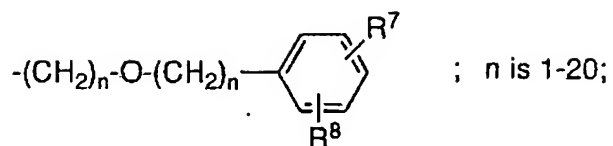


30 ThiosulfatoC₁₋₂₀alkyl of the formula:

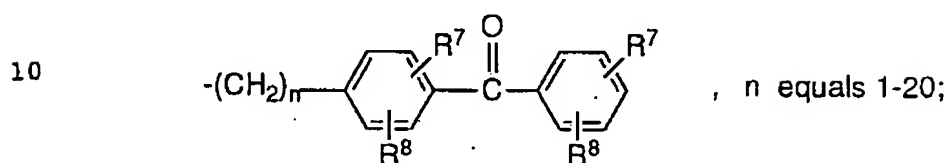


ArylC₁₋₂₀alkyloxyC₁₋₂₀alkyl of the formula:

- 303 -



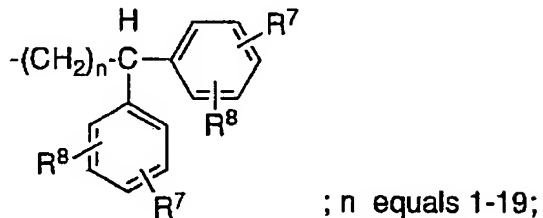
5

ArylcarbonylarylC₁₋₂₀alkyl of the formula:

10

DiarylC₁₋₂₀alkyl of the formula:

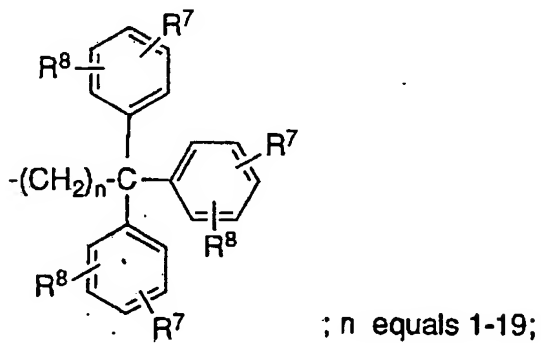
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20

TriarylC₁₋₂₀alkyl of the formula:

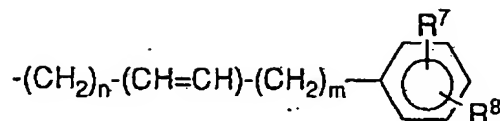
25



30

ArylC₂₋₂₀alkenyl of the formula:

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5

where $n = 0-18$
 $m = 0-18$
 $m + n = 0-18$;

10

 R^4 is

H,
 C_{1-20} alkyl,
 C_6-C_{14} aryl, or
heteroaryl;

15

 R^5 is as defined above and:

H; or
 C_{1-12} alkyl;

20

W is:

O
 $-\text{C}-$, or

25

O
 $-\text{S}-$,
O

30

x is an integer from 1-10;

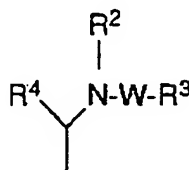
and the dashes a and b indicate double bonds which can be optionally present.

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28. A compound according to Claim 27 and the pharmaceutically acceptable salts thereof, wherein,

5

A is:



10

 R^2 is:

H, or
C₁₋₁₂ alkyl;

15

 R^3 is:

H,
C₁₋₂₀ alkyl,
C₆₋₁₄ aryl,
heteroaryl,
20 C₆₋₁₄ arylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyl,
C₁₋₂₀alkylthioC₁₋₂₀alkyl,
C₁₋₂₀ alkyloxycarbonylC₁₋₂₀ alkyl,
25 carboxylC₁₋₂₀alkyl,
C₁₋₂₀ alkylcarbonylC₁₋₂₀alkyl,
C₃₋₂₀cycloalkyl,
C₃₋₂₀cycloalkylC₁₋₂₀alkyl,
C₆₋₁₄ arylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
30 heteroarylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
haloC₁₋₂₀alkyl,
hydroxyC₁₋₂₀alkyl,
halohydroxyC₁₋₂₀alkyl,
thiosulfatoC₁₋₂₀alkyl,
C₆₋₁₄ arylcarbonylC₆₋₁₄arylC₁₋₂₀alkyl,

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5 C₆₋₁₄ arylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
C₁₋₂₀cycloalkylC₁₋₂₀alkyl,
diarylC₁₋₂₀alkyl,
triarylC₁₋₂₀alkyl,
C₂₋₂₀ alkenyl,

R⁴ is:

10 H,
C₁₋₂₀ alkyl,
C₆₋₁₄ aryl,
heteroaryl;

15 29. A compound according to Claim 28 and the
pharmaceutically acceptable salts thereof wherein:

R² is:

20 H,
methyl,
ethyl,
propyl, linear or branched,
butyl,
pentyl,
hexyl, or
25 heptyl;

R³ is:

30 -t-butyl,
2-thienyl,
-11-(isopropylthio)undecyl,
-7-(carbomethoxy)heptyl,
1-(1-(4-isobutylphenyl)-ethyl),
-7-(carboxy)heptyl,
-acetylmethyl,
-1-adamantylmethyl,

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-2-thienylmethyl,
-2-(carbobenzyloxy)ethyl,
3,4-dimethoxyphenylmethyl,
phenyl,
5 -5-bromopentyl,
-11-hydroxyundecyl,
-1-(4-nitrophenyl)ethyl,
-isopropylthiomethyl,
5-(thiosulfato)pentyl,
10 -benzyloxymethyl,
-carbomethoxymethyl,
-diphenylmethyl,
-triphenylmethyl,
-2-furyl,
15 4-isopropylphenyl,
cyclohexylmethyl,
4-methylcyclohexyl,
3-(3-Indolyl)propyl,
3-Indolylmethyl,
20 4-isobutylbenzyl,
4-nitrobenzyl,
3-acetamidomethyl,
4-ethoxybenzyl,
hexadecyl,
25 Stearyl,
3,5-Bis(trifluoromethyl)benzyl,
3-cyanobenzyl,
heptafluoropropyl,
4-benzoylbenzyl,
30 5-benzotriazolyl,
3,5-difluorobenzyl,
Bis(4-isopropylphenyl)methyl,
2-hydroxybenzyl,
phenylvinyl,

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2-Hydroxy-3,3,3-trichloropropyl,
methyl,
allyl,
n-propyl,
5 n-octyl,
isopropyl,
isobutyl,
ethyl,
benzyl,
10 octadecyl,
2(ethyl)phenyl,
3(chloro)phenyl,
4(methyl)phenyl,
2,3(dichloro)phenyl,
15 4(fluoro)phenyl,
3(methoxy)phenyl,
2(ethoxy)phenyl,
2-naphthyl, or
20 2-thiazolyl;

R⁴ is:

H,
methyl,
ethyl, linear or branched;
25 propyl,
butyl,
C₆₋₁₄ aryl, or
heteroaryl;

30 W is:

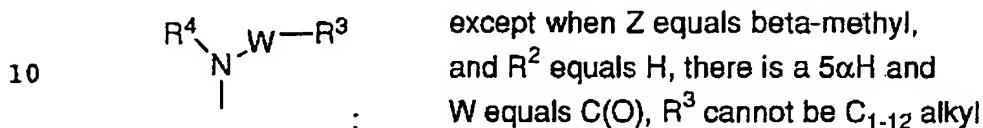
O
- C -, or

O

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- 5 30. A compound according to Claim 27 and the
pharmaceutically acceptable salts thereof,
wherein
A is:



R² is:
15 H, or
C₁₋₁₂ alkyl;

R³ is:
20 H,
C₁₋₂₀ alkyl,
C₆₋₁₄ aryl,
heteroaryl,
amino C₁₋₄alkyl,
mono C₁₋₄alkylaminoC₁₋₄alkyl,
25 di C₁₋₄alkylaminoC₁₋₄alkyl,
C₆₋₁₄ arylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyl,
C₁₋₂₀alkylthioC₁₋₂₀alkyl,
C₁₋₂₀alkylsulfonylC₁₋₂₀alkyl,
30 C₁₋₂₀alkylsulfinylC₁₋₂₀alkyl,
C₁₋₂₀ alkyloxycarbonylC₁₋₂₀alkyl,
carboxyC₁₋₂₀alkyl,
C₁₋₂₀ alkylcarbonylC₁₋₂₀alkyl,
C₁₋₂₀cycloalkyl,
C₁₋₂₀cycloalkylC₁₋₂₀alkyl,

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C₆₋₁₄ arylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
 heteroarylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
 haloC₁₋₂₀alkyl,
 hydroxylC₁₋₂₀alkyl,
 5 halohydroxyC₁₋₂₀alkyl,
 thiosulfatoC₁₋₂₀alkyl,
 C₆₋₁₄ arylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
 C₆₋₁₄ arylcarbonylC₅₋₁₄arylC₁₋₂₀alkyl,
 diarylC₁₋₂₀alkyl,
 10 triarylC₁₋₂₀alkyl,
 C₂₋₂₀ alkenyl,
 C₂₋₂₀ alkenylC₁₋₂₀alkyl,
 heteroarylC₂₋₂₀alkenyl,
 C₆₋₁₄ arylC₂₋₂₀alkenyl,
 15 C₂₋₂₀alkynylC₁₋₂₀alkyl,
 C₆₋₁₄ arylC₂₋₂₀alkynylC₁₋₂₀alkyl, or
 heteroarylC₂₋₂₀alkynylC₁₋₂₀alkyl;

20 W is:

O
 - C -, or

25 O
 - S -
 O

31. A compound according to Claim 30 and the pharmaceutically acceptable salts thereof wherein:

30

R² is:

H,
 methyl,
 ethyl, linear or branched;
 propyl,

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butyl,
pentyl,
hexyl, or
heptyl;

5

R³ is:

-t-butyl,
-2-thienyl,
11-(isopropylthio)undecyl,
-7-(carbomethoxy)heptyl,
1-(1-(4-isobutylphenyl))ethyl,
7-(carboxy)heptyl,
-acetylmethyl,
1-adamantylmethyl,
2-thienylmethyl,
2-(carbobenzyloxy)ethyl,
3,4-dimethoxyphenylmethyl,
phenyl,
5-bromopentyl,
11-hydroxyundecyl,
1-ethyl-4-nitrobenzene-1-yl,
isopropylthiomethyl,
5-(thiosulfato)pentyl,
benzyloxymethyl,
carbomethoxymethyl,
diphenylmethyl,
triphenylmethyl,
2-furyl,
4-isopropylphenyl,
cyclohexylmethyl,
4-methylcyclohexyl,
3-(3-Indolyl)propyl,
3-Indolylmethyl,
4-isobutylbenzyl,

10

15

20

25

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4-nitrobenzyl,
 3-acetamidomethyl,
 4-ethoxybenzyl,
 5 hexadecyl,
 stearyl,
 3,5-Bis(trifluoromethyl)benzyl,
 3-cyanobenzyl,
 heptafluoropropyl,
 10 4-benzoylbenzyl,
 5-benzotriazolyl,
 3,5 difluorobenzyl,
 Bis(4-isopropylphenyl)methyl,
 2-hydroxybenzyl,
 15 phenylvinyl, or
 2-hydroxy-3,3,3-trichloropropyl;

W is:

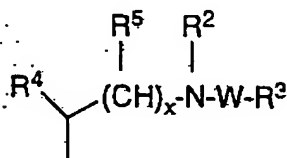
O
 20 - C -, or

O
 - S -
 O

25

32. A compound according to Claim 27 and the
 pharmaceutically acceptable salts thereof,
 wherein:

30 A is:



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R² is:

H, or
C₁₋₁₂ alkyl;

5

R³ is:

H,
C₁₋₂₀ alkyl,
C₆₋₁₄ aryl,
heteroaryl,
C₆₋₁₄ arylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyl,
C₁₋₂₀alkylthioC₁₋₂₀alkyl,
C₁₋₂₀alkylsulfinylC₁₋₂₀alkyl,
C₁₋₂₀alkylsulfonylC₁₋₂₀alkyl,
C₁₋₂₀ alkyloxycarbonylC₁₋₂₀alkyl,
carboxyC₁₋₂₀alkyl,
C₁₋₂₀ alkylcarbonylC₁₋₂₀alkyl,
C₁₋₂₀cycloalkyl,
C₁₋₂₀cycloalkylC₁₋₂₀alkyl,
C₆₋₁₄ arylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
haloC₁₋₂₀alkyl,
hydroxylC₁₋₂₀alkyl,
halohydroxylC₁₋₂₀alkyl,
thiosulfatoC₁₋₂₀alkyl,
C₆₋₁₄ arylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
C₆₋₁₄ arylcarbonylC₅₋₁₄arylC₁₋₂₀alkyl,
diarylC₁₋₂₀alkyl,
triarylC₁₋₂₀alkyl,
C₂₋₂₀ alkenyl,
C₂₋₂₀ alkenylC₁₋₂₀alkyl,
heteroarylC₂₋₂₀alkenyl,
C₆₋₁₄ arylC₂₋₂₀alkenyl,

10

15

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25

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C₂₋₂₀alkynylC₁₋₂₀alkyl,
C₆₋₁₄ arylC₂₋₂₀alkynylC₁₋₂₀alkyl, or
heteroarylC₂₋₂₀alkynylC₁₋₂₀alkyl;

5

R⁴ is:

H,
C₁₋₂₀ alkyl,
C₆₋₁₄ aryl or
heteroaryl;

10

R⁵ is defined above and is:

H, or
C₁₋₂₀ alkyl;

15

W is:

O
- C -, or

20

O
- S -
O

x is an integer from 1-10.

25

33. A compound according to Claim 32 and the
pharmaceutically acceptable salts thereof, wherein

R² is:

30

H,
methyl,
ethyl, linear or branched,
propyl,
butyl,
pentyl,

- 315 -

hexyl, or
heptyl;

R³ is:

- 5 t-butyl,
 2-Thienyl,
 11-(isopropylthio)undecyl,
 7-(carbomethoxy)heptyl,
10 1-(1-(4-isobutylphenyl))ethyl,
 7-(carboxy)heptyl,
 acetylmethyl,
 1-adamantylmethyl,
 2-thienylmethyl,
15 2(carbobenzyloxy)ethyl,
 3,4-dimethoxyphenylmethyl,
 phenyl,
 5-bromopentyl,
 11-hydroxyundecyl,
20 -1(4-nitrophenyl)ethyl,
 isopropylthiomethyl,
 5-(thiosulfato)pentyl,
 benzyloxymethyl,
 carbomethoxymethyl,
25 diphenylmethyl,
 triphenylmethyl,
 2-furyl,
 4-isopropylphenyl,
 cyclohexylmethyl,
30 4-methylcyclohexyl,
 3-(3-Indolyl)propyl,
 3-Indolylmethyl,
 4-Isobutylbenzyl,
 3-acetamidomethyl,
 4-ethoxybenzyl,

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5 hexadecyl,
stearyl,
3,5 Bis(trifluoromethyl)benzyl,
3-cyanobenzyl,
heptafluoropropyl,
4-benzoylbenzyl,
5-benzotriazolyl,
3,5-difluorobenzyl,
10 Bis (4-isopropylphenyl)methyl,
2-hydroxybenzyl,
phenylvinyl, or,
2-hydroxy-3,3,3-trichloropropyl;

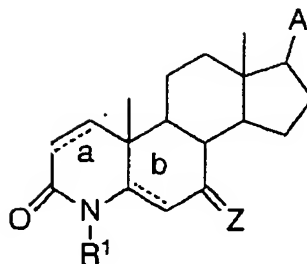
15 R⁴ is:
H,
methyl,
ethyl, linear or branched;
propyl,
butyl,
20 C₆₋₁₄ aryl, or
heteroaryl;

R⁵ is:
25 H,
methyl,
ethyl,
propyl,
butyl, or
30 pentyl.

34. A compound of Claim 1 of the formula:

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5



10

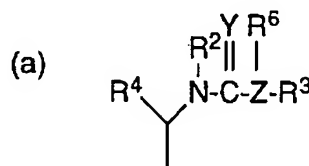
and the pharmaceutically acceptable salts thereof,

wherein:

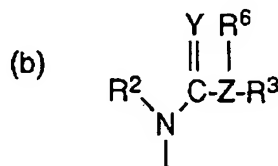
7=Z is defined in Claim 1 and dashed lines a and b can independently represent double bonds:

15

A is:



20

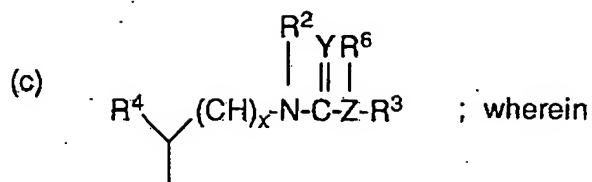


25

30

except when Z is beta-methyl R² equals H, Y equals O, Z equals N and there is 5αH, R⁶ and R³ cannot be independently selected from H, C₁₋₈ alkyl, C₃₋₆ cycloalkyl, phenyl and R⁶ and R³ cannot be taken together with the adjacent N to form a 5-6 membered ring comprising up to one other heteroatom selected from O or N, or

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R² is:

H, or
C₁₋₂₀ alkyl;

R³ is:

H,
amino,
mono C₁-C₄ alkylamino,
di C₁-C₄ alkylamino,
mono C₁-C₄ alkylaminoaryl,
di C₁-C₄ alkylaminoaryl,
C₁₋₂₀ alkyl,
C₆₋₁₄ aryl,
heteroaryl,
C₆₋₁₄ arylC₁₋₂₀alkyl,
C₃₋₂₀ cycloalkyl,
C₃₋₂₀ cycloalkylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyl,
C₂₋₂₀ alkenylC₁₋₂₀alkyl,
haloC₁₋₂₀alkyl,
C₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
C₁₋₂₀ alkyloxyC₁₋₂₀alkyl,
carboxyC₁₋₂₀alkyl,
C₆₋₁₄ arylcarbonylC₅₋₁₄arylC₁₋₂₀alkyl,
C₁₋₂₀ alkylcarbonylC₁₋₂₀alkyl,
C₆₋₁₄ arylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
hydroxylC₁₋₂₀alkyl,

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halohydroxylC₁₋₂₀alkyl,
C₆₋₁₄ arylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
diarylC₁₋₂₀alkyl,
5 triarylC₁₋₂₀alkyl,
C₂₋₂₀ alkenyl,
C₂₋₂₀ alkenylC₁₋₂₀alkyl,
C₂₋₂₀ alkynylC₁₋₂₀alkyl,
10 C₆₋₁₄ arylC₂₋₂₀alkynylC₁₋₂₀alkyl,
heteroarylC₂₋₂₀alkynylC₁₋₂₀alkyl,
C₁₋₂₀ alkylthioC₁₋₂₀alkyl,
C₁₋₂₀ alkylsulfonylC₁₋₂₀alkyl, or
C₁₋₂₀ alkylsulfinyl C₁₋₂₀alkyl;

15 R⁴ is:

H,
C₁₋₂₀ alkyl,
heteroaryl, or
20 C₆₋₁₄ aryl;

R⁵ can be the same or different when X is greater than 1 and is:

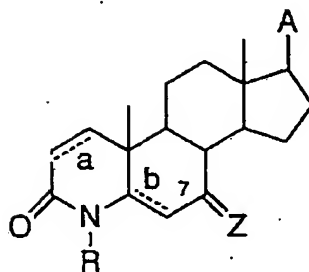
H,
25 C₁₋₂₀ alkyl,
heteroaryl, or
C₆₋₁₄ aryl;

R⁶ is present when Z equals N and is independently

30 H,
C₁₋₂₀ alkyl, or
equivalent to R³; or taken together with R³ and the N to which
they are
attached represent a heteroaryl ring system:

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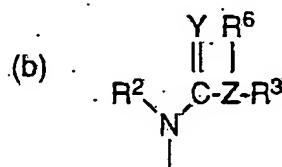
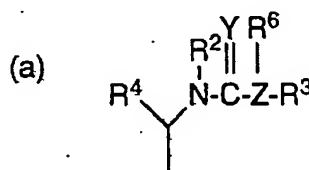
35. A compound according to Claim 34 of the formula:



and the pharmaceutically acceptable salts thereof,
wherein:

15 7=Z is defined in Claim 1:

A is:

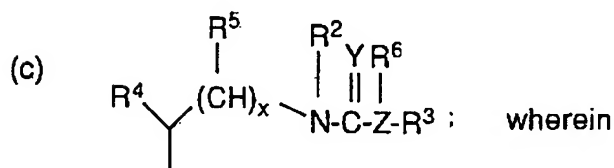


except when 7=Z equals 7 β -methyl and R² equals H, Y equals O, Z equals N and there is a 5a H, R⁶ and R³ cannot be independently selected from H, C₁₋₈ alkyl, C₃₋₆ cycloalkyl, phenyl and R⁶ and R³ cannot be taken together with the adjacent N to

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form a 5-6 membered ring comprising up to one other heteroatom selected from O or N; or

5



10

R² is:

H, or
C₁₋₂₀ alkyl;

15

R³ is:

H,
C₁₋₂₀ alkyl further comprising a straight or
branched chain alkane of up to 20 carbon atoms;

20

C₆₋₁₄ aryl wherein aryl comprises a mono or polycyclic
system composed of 6-membered aromatic rings either
unsubstituted or substituted with R wherein R comprises
H, C₁₋₂₀ alkyl, arylC₁₋₂₀alkyl with the alkyl groups
unsubstituted or substituted with hydroxyl, C₁₋₈
alkyloxy, carboxy C₁₋₁₀alkyl, or halogen; or

25

aryl is directly substituted or multisubstituted independently
with hydroxyl, haloC₁₋₂₀alkyl, benzoyl, C₁₋₂₀alkyloxy,
C₁₋₂₀alkyl, C₂₋₂₀alkenyl, cyano, nitro, carboxamido,
acetamido, or halogen;

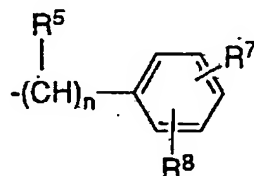
30

heteroaryl, which comprises a mono or polycyclic system
composed of 5- and 6-membered aromatic rings
containing 1, 2, 3 or 4 heteroatoms chosen from N, O,
or S and either unsubstituted or substituted with R as

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defined for aryl or substituted or multisubstituted independently with hydroxyl, C₁-20 alkyloxy, C₁-20 alkyl, benzyl, amino, mono C₁-C₄ or di C₁-C₄ alkylamino, carboxamido, acetamido, C₂-20 alkenyl, cyano, nitro, haloC₁-20 alkyl, or halogens, directly bonded to the aromatic carbon atom(s);

arylC₁-20 alkyl of the formula:



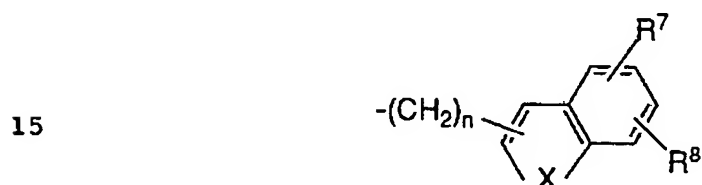
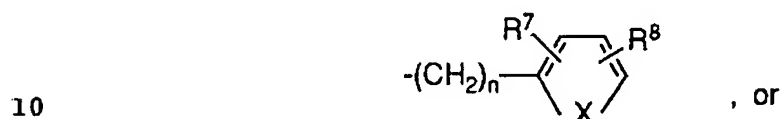
wherein the aromatic ring is optionally and independently substituted with R⁷ and R⁸ wherein R⁷ and R⁸ comprise

H,
CH₃,
C₂H₅,
carboxamide,
OH,
OCH₃,
NO₂,
CN,
F,
RS, RSO, RSO₂, R₂N, where R can be the same or different and is selected from: H, C₁-C₄ alkyl, C₆-C₁₀ aryl;
Cl,
acetamido,
OC₂H₅,
CF₃,
isopropyl, or

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isobutyl; n equals 1-10 and the C₁₋₂₀alkyl portion is
optionally
substituted with R⁷;

5 HeteroarylC₁₋₂₀alkyl further comprising the formula:



wherein X equals O, S, or NR; and n equals 1-20;

20 C₁₋₂₀alkylsulfonylC₁₋₂₀alkyl,
C₁₋₂₀alkylthioC₁₋₂₀alkyl,
C₁₋₂₀alkylsulfinylC₁₋₂₀alkyl, comprising the formula:
-(CH₂)_nS(O)_p-R⁹ wherein R⁹ comprises

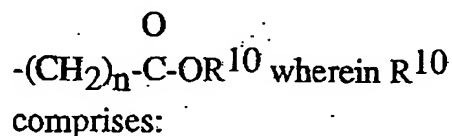
25 CH₃,
C₂H₅,
C₃H₇,
C₄H₉,
30 isopropyl,
isobutyl,
sec-butyl,
t-butyl,
isopentyl,
neopentyl, or

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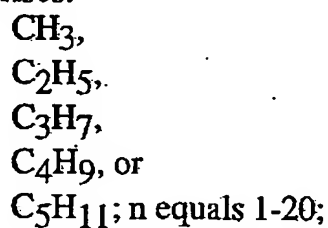
isohexyl; n equals 1-20; p = 0, 1, or 2;

C₁₋₂₀ alkyloxycarbonylC₁₋₂₀alkyl further comprising the formula:

5

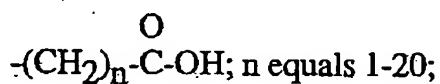


10



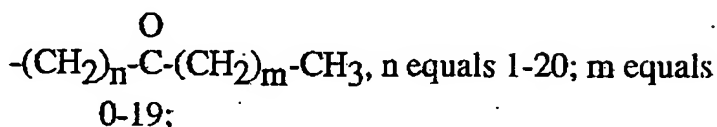
15

carboxylC₁₋₂₀ alkyl further comprising:



20

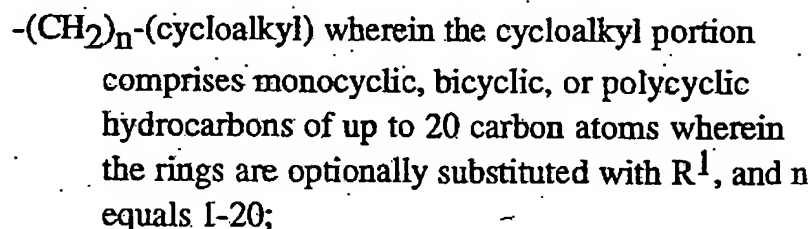
C₁₋₂₀alkylcarbonylC₁₋₂₀ alkyl further comprising



25

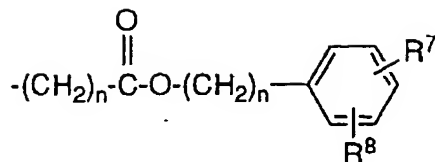
C₁₋₂₀ cycloalkylC₁₋₂₀ alkyl of the formula:

30



ArylC₁₋₂₀ alkyloxycarbonylC₁₋₂₀ alkyl of the formula:

- 325 -

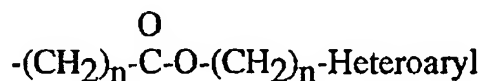


5

wherein R^7 and R^8 are as defined; n equals 1-20;

Heteroaryl C_{1-20} alkyloxycarbonyl C_{1-20} alkyl of the formula:

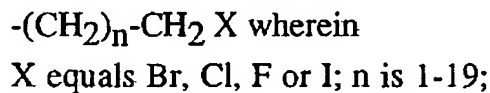
10



wherein Heteroaryl is as defined; n equals 1-20;

15

halo C_{1-20} alkyl of the formula:



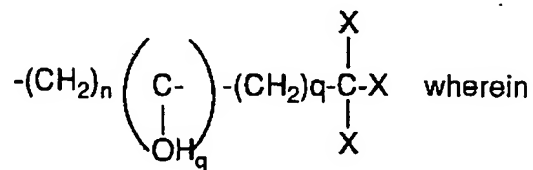
20

hydroxyl C_{1-20} alkyl of the formula:



25

halohydroxyl C_{1-20} alkyl of the formula:



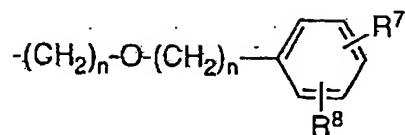
30

X equals Br, Cl, F or I; n is 0-18, q is 0-18, n + q = 0-18;

Aryl C_{1-20} alkyloxy C_{1-20} alkyl of the formula:

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5

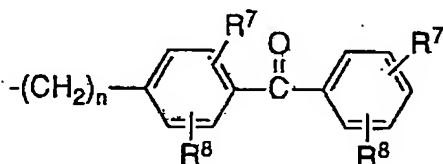


wherein

R^7 and R^8 are as defined; n is 1-20;

10

Arylcarbonylaryl C_{1-20} alkyl of the formula:

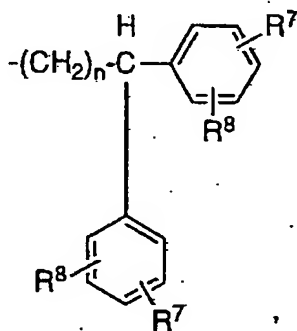


15

, n equals 1-20;

Diaryl C_{1-20} alkyl of the formula:

20



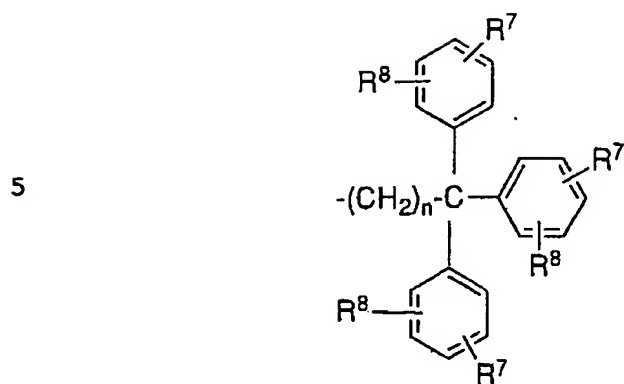
25

, n equals 1-19;

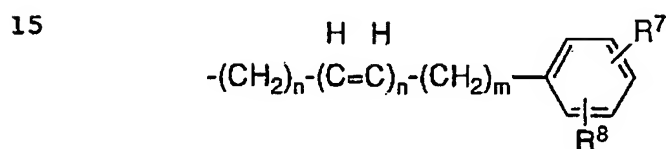
Triaryl C_{1-20} alkyl of the formula:

30

- 327 -



, n equals 1-19;

ArylC₂₋₂₀ alkenyl of the formula:

, n equals 0-18;
 n equals 0-18
 m + n equals 0-18;

R⁴ is:

25 H,
 C₁₋₂₀alkyl,
 C₆₋₁₄ aryl, or
 Heteroaryl;

R⁵ is as defined above and is:

30 H, or
 C₁₋₁₂ alkyl;

R⁶ is present when Z equals N and is independently

H,

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C₁₋₂₀ alkyl,
 equivalent to R³; or taken together with R³ and the N to which
 they are attached represent a heteroaryl ring system;

5

Y is:

O, or
 S;

10

Z is

N, or
 O;

15

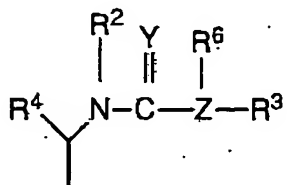
x is an integer from 1-10, and

dashes a and b indicate double bonds which can be optionally present.

36. A compound according to Claim 35 and the
 pharmaceutically acceptable salts thereof, wherein:

20

A is



25

; wherein

R² is:

H, or
 C₁₋₂₀ alkyl;

30

R³ is:

H,
 C₁₋₂₀ alkyl,
 C₆₋₁₄ arylC₁₋₂₀alkyl,
 C₃₋₂₀ cycloalkyl;

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C₃₋₂₀ cycloalkylC₁₋₂₀alkyl,
 heteroarylC₁₋₂₀alkyl,
 C₁₋₂₀alkylcarbonylC₁₋₂₀alkyl,
 5 C₆₋₁₄ arylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
 carboxyC₁₋₂₀alkyl,
 heteroarylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
 hydroxyC₁₋₂₀alkyl,
 C₆₋₁₄ arylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
 10 heteroaryl,
 C₆₋₁₄ aryl,
 C₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
 C₂₋₂₀ alkenylC₁₋₂₀alkyl,
 C₆₋₁₄ arylcarbonylarylC₁₋₂₀alkyl,
 15 halohydroxylC₁₋₂₀alkyl,
 diarylC₁₋₂₀alkyl,
 triarylC₁₋₂₀alkyl,
 halo C₁₋₂₀alkyl,
 C₁₋₂₀ alkyloxyC₁₋₂₀alkyl,
 20 C₁₋₂₀ alkylthioC₁₋₂₀alkyl,
 C₁₋₂₀ alkylsulfonylC₁₋₂₀alkyl, or
 C₁₋₂₀ alkylsulfinylC₁₋₂₀alkyl;

R⁴ is:

25 H,
 C₁₋₂₀ alkyl,
 heteroaryl, or
 C₆₋₁₄ aryl;

30 R⁶ is present when Z equals N and is:

H,
 equivalent to R³, or
 C₁₋₂₀ alkyl; or taken together with R³ and the N to which
 they are attached represent a heteroaryl ring system;

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Y is:

O,
S;

5

Z is:

N, or
O.

10

37. A compound according to Claim 36 and the
pharmaceutically acceptable salts thereof, wherein:

R² is:

15

H,
CH₃,
C₂H₅, linear or branched;
C₃H₇,
C₄H₉,
C₅H₁₁,
C₆H₁₃, or
20 C₇H₁₅;R³ is:

25

-t-butyl,
-2-thienyl,
-11-(isopropylthio)undecyl,
-7-(carbomethoxy)heptyl,
1-(1-(4-isobutylbenzene))ethyl,
-7-(carboxy)heptyl,
-acetylmethyl,
30 -1-adamantylmethyl,
-2-thienylmethyl,
-2-(carbobenzyloxy)ethyl,
-3,4 dimethoxyphenylmethyl,
-phenyl,

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5 -5-bromopentyl,
 -11-hydroxyundecyl,
 -1(4-nitrophenyl)ethyl,
 -isopropylthiomethyl,
 -benzyloxymethyl,
 -carbomethoxymethyl,
 -diphenylmethyl,
 -triphenylmethyl,
10 -2-furyl,
 4-isopropylphenyl,
 cyclohexylmethyl,
 4-methylcyclohexyl,
 3-(3-Indolyl)propyl,
15 3-Indolylmethyl,
 4-isobutylbenzyl,
 4-nitrobenzyl,
 3-acetamidomethyl,
 4-ethoxybenzyl,
20 hexadecyl,
 stearyl,
 3,5 Bis(trifluoromethyl),
 3-cyanobenzyl,
 heptafluoropropyl,
25 4-benzoylbenzyl,
 5-benzotriazolyl,
 3,5 difluorobenzyl,
 Bis(4-isopropylphenyl) methyl,
 2-hydroxybenzyl,
30 methyl,
 allyl,
 n-propyl,
 n-octyl,
 isopropyl,
 isobutyl,

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ethyl,
benzyl,
octadecyl,
2(ethyl)phenyl,
5 3(chloro)phenyl,
4(methyl)phenyl,
2,3(dichloro)phenyl,
4(floro)phenyl,
3(methoxy)phenyl,
10 2(ethoxy)phenyl,
2(napthyl), or
2-thiazolyl.

15 R⁴ is:
H,
methyl,
ethyl, linear or branched;
propyl,
butyl,
20 C₆₋₁₄ aryl, or
heteroaryl;

R⁶ is present when Z equals N and is:
25 H,
equivalent to R³, or
C₁₋₂₀ alkyl; or taken together with R³ and the N to which
they are attached represent a heteroaryl ring system;

30 Y is:
O, or
S;

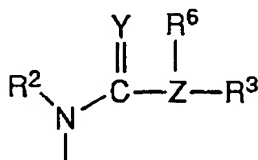
Z is:
O, or

- 333 -

N.

38. A compound according to Claim 35 and the
pharmaceutically acceptable salts thereof, wherein:

A is



except when R² equals H, Y equals O and Z equals N
and there is a 5αH, R⁶ and R³ cannot be
independently selected from H, C₁₋₈alkyl, C₃₋₆cycloalkyl, phenyl and R⁶ and R³ cannot be
taken together with the adjacent N to form a 5-6
membered ring comprising up to one other
heteroatom selected from O or N;

wherein

R² is:

H, or
C₁₋₁₂ alkyl;

R³ is:

H,
C₁₋₂₀ alkyl,
C₆₋₁₄ arylC₁₋₂₀alkyl,
C₃₋₂₀cycloalkyl,
C₃₋₂₀cycloalkylC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyl,
C₁₋₂₀alkylcarbonylC₁₋₂₀alkyl,

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C₆₋₁₄ arylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
 carboxyC₁₋₂₀alkyl,
 heteroarylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
 hydroxyC₁₋₂₀alkyl,
 5 C₆₋₁₄ arylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
 heteroaryl,
 C₆₋₁₄ aryl,
 C₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
 10 C₆₋₁₄ arylcarbonylarylC₁₋₂₀alkyl,
 halohydroxylC₁₋₂₀alkyl,
 diarylC₁₋₂₀alkyl,
 triarylC₁₋₂₀alkyl,
 C₂₋₂₀ alkenylC₁₋₂₀alkyl,
 haloC₁₋₂₀alkyl,
 15 C₁₋₂₀ alkyloxyC₁₋₂₀alkyl,
 C₂₋₂₀alkenylC₁₋₂₀alkyl,
 C₁₋₂₀ alkylthioC₁₋₂₀alkyl,
 C₁₋₂₀ alkylsulfonylC₁₋₂₀alkyl, or
 20 C₁₋₂₀ alkylsulfinylC₁₋₂₀alkyl;

R⁶ is present when Z equals N and is:

H,
 equivalent to R³, or
 25 C₁₋₂₀ alkyl; or taken together with R³ and the N to which
 they are attached represent a heteroaryl ring system;

Y is:

O, or
 30 S;

Z is:

N, or
 O.

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39. A compound according to Claim 38 and the pharmaceutically acceptable salts thereof, wherein

R² is:

5

H, or
C₁₋₁₂ alkyl;

R³ is:

10

-t-butyl,
-2-thienyl,
11-(isopropylthio)undecyl,
-7-(carbomethoxy)heptyl,
1-(1-(4-isobutylphenyl))ethyl,
-7-(carboxy)heptyl,
15 -acetylmethyl,
-1-adamantylmethyl,
-2-thienylmethyl,
-2-(carbobenzyloxy)ethyl,
-3,4 dimethoxyphenylmethyl,
20 -phenyl,
-5-bromopentyl,
-11-hydroxyundecyl,
-1(4-nitrophenyl)ethyl,
-isopropylthiomethyl,
25 -benzyloxymethyl,
-carbomethoxymethyl,
-diphenylmethyl,
-triphenylmethyl,
-2-furyl,
30 4-isopropylphenyl,
cyclohexylmethyl,
4-methylcyclohexyl,
3-(3-Indolyl)propyl,
3-Indolylmethyl,

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4-isobutylbenzyl,
4-nitrophenylbenzyl,
3-acetamidomethyl,
4-ethoxybenzyl,
5 hexadecyl,
stearyl,
3,5 Bis(trifluoromethyl),
3-cyanobenzyl,
10 heptafluoropropyl,
4-benzoylbenzyl,
5-benzotriazolyl,
3,5 difluorobenzyl,
Bis(4-isopropylphenyl) methyl,
15 2-hydroxybenzyl,
methyl,
allyl,
n-propyl,
n-octyl,
20 isopropyl,
sobutyl,
ethyl,
benzyl,
octadecyl,
25 2(ethyl)phenyl,
3(chloro)phenyl,
4(methyl)phenyl,
2,3(dichloro)phenyl,
4(fluoro)phenyl,
30 3(methoxy)phenyl,
2(ethoxy)phenyl,
2(naphthyl) or,
2-thiazolyl,

R⁶ is present when Z equals N and is:

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H,
 equivalent to R^3 , or
 C_{1-20} alkyl; or taken together with R^3 and the N to which
 they are attached represent a heteroaryl ring system;

Y is:

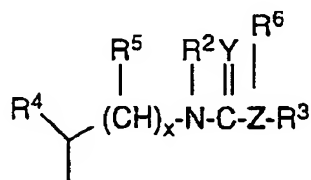
O, or
 S;

Z is:

N, or
 O.

40. A compound according to Claim 35 and the
 pharmaceutically acceptable salts thereof, wherein:

A is:



; wherein

 R^2 is:

H, or
 C_{1-12} alkyl;

 R^3 is:

H,
 C_{1-20} alkyl,
 C_{6-14} aryl C_{1-20} alkyl,
 C_{3-20} cycloalkyl,
 C_{3-20} cycloalkyl C_{1-20} alkyl,

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heteroarylC₁₋₂₀alkyl,
C₁₋₂₀alkylcarbonylC₁₋₂₀alkyl,
C₆₋₁₄ arylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
5 carboxyC₁₋₂₀alkyl,
heteroarylC₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
hydroxyC₁₋₂₀alkyl,
C₆₋₁₄ arylC₁₋₂₀alkyloxyC₁₋₂₀alkyl,
C₁₋₂₀alkyloxycarbonylC₁₋₂₀alkyl,
10 C₆₋₁₄ arylcarbonylarylC₁₋₂₀alkyl,
halohydroxylC₁₋₂₀alkyl,
diarylC₁₋₂₀alkyl,
triarylC₁₋₂₀alkyl,
C₂₋₂₀alkenylC₁₋₂₀alkyl,
15 heteroaryl,
C₆₋₁₄ aryl,
C₂₋₂₀alkenylC₁₋₂₀alkyl,
haloC₁₋₂₀alkyl,
C₁₋₁₂ alkyloxyC₁₋₂₀alkyl,
20 C₁₋₁₃ alkylthioC₁₋₂₀alkyl,
C₁₋₁₃ alkylsulfonylC₁₋₂₀alkyl, or
C₁₋₁₃ alkylsulfinylC₁₋₂₀alkyl;

R⁴ is:

25 H,
C₁₋₁₃ alkyl,
heteroaryl, or
C₆₋₁₄ aryl;

30 R⁵ is defined above and is:

H,
C₁₋₁₃ alkyl,
heteroaryl, or
C₆₋₁₄ aryl;

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R^6 is present when Z equals N and is:

H,
equivalent to R^3 , or
5 C_{1-20} alkyl; or taken together with R^3 and the N to which
they are attached represent a heteroaryl ring system;

Y is:

O, or
10 S;

Z is:

N, or
O;

15

x is an integer from 1-10.

41. A compound according to Claim 40 and the
pharmaceutically acceptable salts thereof, wherein

20

R^2 is:

H, or
 C_{1-12} alkyl;

25

R^3 is

-t-butyl,
-2-thienyl,
-11-(isopropylthio)undecyl,
-7-(carbomethoxy)heptyl,
30 1-(1-(4-isobutylbenzene))ethyl,
-7-(carboxy)heptyl,
-acetylmethyl,
-1-adamantylmethyl,
-2-thienylmethyl,
-2-(carbobenzyloxy)ethyl,

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-3,4 dimethoxyphenylmethyl,
-phenyl,
-5-bromopentyl,
-11-hydroxyundecyl,
5 -1(4-nitrophenyl)ethyl,
-isopropylthiomethyl,
5-(thiosulfato)pentyl,
-benzyloxymethyl,
10 -carbomethoxymethyl,
-diphenylmethyl,
-triphenylmethyl,
-2-furyl,
4-isopropylphenyl,
15 cyclohexylmethyl,
4-methylcyclohexyl,
3-(3-Indolyl)propyl,
3-Indolylmethyl,
4-isobutylbenzyl,
4-nitrophenylbenzyl,
20 3-acetamidomethyl,
4-ethoxybenzyl,
hexadecyl,
stearyl,
25 3,5 Bis(trifluoromethyl),
3-cyanobenzyl,
heptafluoropropyl,
4-benzoylbenzyl,
5-benzotriazole,
3,5 difluorobenzyl,
30 Bis(4-isopropylphenyl) methyl,
2-hydroxybenzyl,
methyl,
allyl,
n-propyl,

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5 n-octyl,
isopropyl,
isobutyl,
ethyl,
benzyl,
octadecyl,
2(ethyl)phenyl,
3(chloro)phenyl,
10 4(methyl)phenyl,
2,3(dichloro)phenyl,
4(floro)phenyl,
3(methoxy)phenyl,
2(ethoxy)phenyl,
15 2(naphthyl), or
2-thiazolyl.

R⁴ is:

20 H,
C₁₋₁₃ alkyl,
heteroaryl, or
C₆₋₁₄ aryl;

R⁵ is defined above and is:

25 H,
C₁₋₁₃ alkyl,
heteroaryl, or
C₆₋₁₄ aryl;

30 R⁶ is present when Z equals N and is:

H,
equivalent to R³, or
C₁₋₂₀ alkyl; or taken together with R³ and the N to which
they are attached represent a heteroaryl ring system;

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Y is:

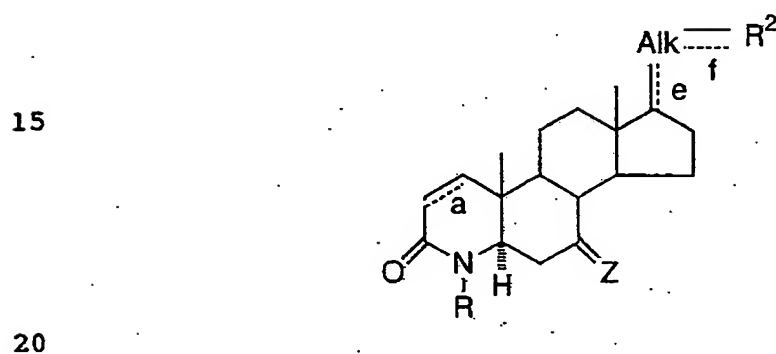
O, or
S;

5 Z is:

N, or
O;

10 x is an integer from 1-10.

42. A compound of Claim 1 of the formula:



Z is defined above in Claim 1:

25 Alk is C₁-C₄ straight or branched chain alkyl or alkenyl;
dashed lines a, e and f each can independently represent
a double bond when present, with the proviso that
double bonds formed by e and f are not both present
concurrently;

30 R is selected from hydrogen, methyl or ethyl;

R² is (a) C₆-C₁₀ aryl, cyano or 5-6 membered heteroaryl
radical which can contain 1-4 nitrogen atoms, one
oxygen or sulfur atoms or combinations thereof with 1-

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2 nitrogen atoms, providing that where R^2 is cyano, double bonds e and f are not present,

5 (b) COR_1 , where R_1 is C_6-C_{10} aryl, substituted C_6-C_{10} aryl, and heteroaryl;

(c) $CONHR_2$, where R_2 is substituted phenyl, heteroaryl, substituted heteroaryl or C_7 to C_{12} cycloalkyl;

10 (d) CO_2R_3 , where R_3 is C_1-C_{18} liner or branched alkyl, C_6-C_{10} aryl substituted C_6-C_{10} aryl, or C_7-C_{12} cycloalkyl; providing that in (b), (c) or (d), Alk is only alkenyl;

15 wherein the above aryl or heteroaryl radicals can also be fused with a benzo or another heteroraryl ring and can further be substituted with one or more substituents; and pharmaceutically acceptable salts and esters thereof.

20 43. The compound of Claim 42 wherein said aryl radical is selected from phenyl, benzyl and naphthyl.

25 44. The compound of Claim 42 wherein the heteroaryl radical is selected from:

30 pyridyl, pyrrol, thienyl, isothiazolyl, thiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, isoxazolyl, triazolyl, furanyl, oxazolyl, or

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thiadiazolyl.

45. The compound of Claim 42 wherein said aryl or heteroaryl substituents are selected from:

5 hydrogen;

C₁₋₈ straight or branched alkyl;

C₂₋₈ straight or branched alkenyl;

C₃₋₈ cycloalkyl;

C₂₋₈ alkynyl;

10 -CONR⁴R⁵ where R⁴ and R⁵ independently are H, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, C₁₋₄ perhaloalkyl, phenyl, or substituted phenyl, as described below;

15 -COR⁴;

-S(O)_nR⁴ where n=0-2;

-OCOR⁴;

-SO₂NR⁴R⁵;

-NR⁴(CO)R⁵;

20 -NR⁴(CO)NHR⁵;

-NHSO₂R⁴;

-OR⁴;

-NR⁴R⁵;

CN;

25 NO₂;

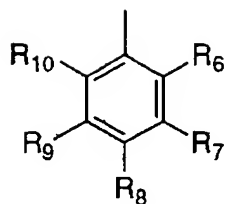
halo;

perhalo C₁-C₄alkyl;

-CO₂R⁴;

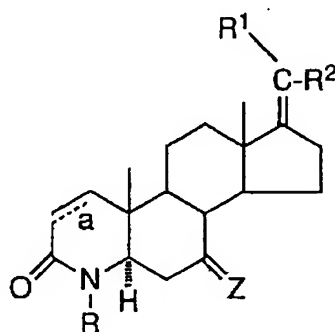
30 phenyl or substituted phenyl of the formula:

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where R⁶-R¹⁰ independently represent one or more of the substituents as defined above.

46. The compound of Claim 42 of the formula:



wherein Z is defined in Claim 1 and the dashed line a represents a double bond when present,

R and R¹ are selected from hydrogen, methyl and ethyl; and

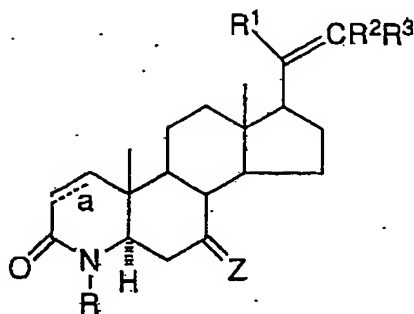
R² is as defined in Claim 42, including both (E) and (Z) forms, and mixtures thereof.

47. The compound of Claim 46 wherein R¹ is methyl.

48. The compound of Claim 46 wherein R¹ is hydrogen.

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49. A compound of Claim 42 of the formula:



wherein: Z is defined in Claim 1;
the dashed line a can represent a double bond when present,
R, R¹ and R³ are

independently selected from hydrogen, methyl and
ethyl, with the
proviso that at least one of R¹ and R³ is hydrogen,

R² is C₆-C₁₀ aryl or heteroaryl as defined in Claim 1, and R² and
R³ can be in a E or Z bond configuration, and mixtures
thereof.

50. The compound of Claim 49 wherein R¹ and R³
are both hydrogen.

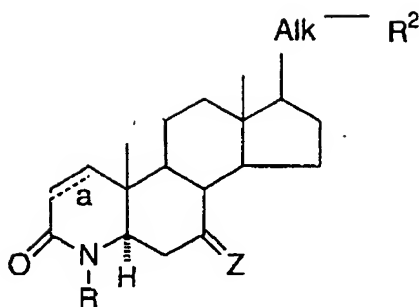
51. The compound of Claim 49 wherein R¹ is methyl
or ethyl and R³ is hydrogen.

52. The compound of Claim 49 wherein R¹ is
hydrogen and R³ is methyl or ethyl.

53. The compound of Claim 42 of the following
formula.

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5



10 wherein: Z is defined in Claim 1:

Alk is C₁-C₄ straight or branched chain alkyl; dashed line a
can represent a double bond when present;

15 R is selected from hydrogen, methyl or ethyl;

R² is (a) C₆-C₁₀ aryl, cyano, or 5-6 membered heteroaryl
radical which can contain 1-4 nitrogen atoms, one
oxygen or sulfur atoms or combinations thereof with 1-
2 nitrogen atoms;

20

(b) COR₁, where R₁ is C₆-C₁₀ aryl, substituted C₆-C₁₀
aryl, and heteroaryl;

25

(c) CONHR₂, where R₂ is substituted phenyl,
heteroaryl, substituted heteroaryl, or C₇ to C₁₂
cycloalkyl;

30

(d) CO₂R₃, where R₃ is C₁-C₁₈ linear or branched
alkyl, C₆-C₁₀ aryl, substituted C₆-C₁₀ aryl, or
C₇-C₁₂ cycloalkyl; providing that in (b), (c) or
(d), Alk is only alkenyl;

wherein the above aryl or heteroaryl radicals can also be fused with
a benzo or another heteroaryl ring and can further be substituted

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with one or more substituents; and pharmaceutically acceptable salts and esters thereof.

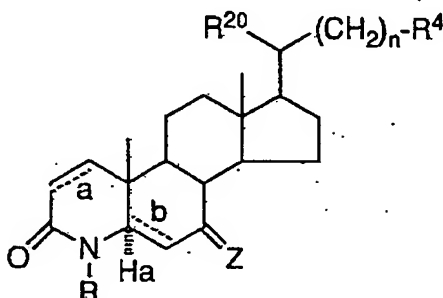
5 54. The compound of Claim 53 wherein said Alk and R^2 are of the combined structure:

-CH₂R², -CH(CH₃)R², -CH₂CH₂R², -CH(CH₃)CH₂R²,
-CH(CH₃CH₂)CH₂R², CH₂CH(CH₃)R², CH₂CH₂CH₂R², or
-CH₂CH₂CH₂CH₂R².

10

55. A compound according to Claim 1 of the formula:

15



20

wherein

R is selected from hydrogen, methyl or ethyl; the
25 dashed lines a and b, indicate double bonds which can be
present providing that when b is present, the 5α
hydrogen, Ha is absent;

Z can be

30

- 1) oxo,
- 2) α-hydrogen and a β-substituent selected from: C₁-C₄ alkyl,
C₂-C₄ alkenyl, CH₂COOH, hydroxy, carboxy, COOC₁-
C₄ alkyl esters, OCONR¹R², where R¹ and R² are
independently H, C₁-C₄ alkyl, phenyl, benzyl, and R¹

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and R^2 together with the N can form a 5-6 membered saturated heterocyclic ring, optionally with one other heteroatom; OC_1-C_4 alkyl, OC_3-C_6 cycloalkyl, -OCOCH₃, halo, hydroxy C_1-C_2 alkyl, halo C_1-C_2 alkyl or trifluoromethyl, C_3-C_6 cycloalkyl;

3) =CH-R' where R' is H, C_1-C_4 alkyl;

4) spiro:



where:

15 R^{20} is H, methyl;

n is 0-10;

R^4 is selected from:

(a) -COR¹, where R^1 is phenyl or substituted phenyl;

20 (b) -CONHR², where R^2 is substituted phenyl, heteroaryl, substituted heteraryl;

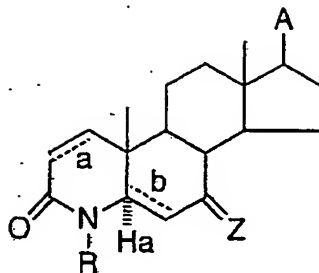
(c) -COOR³, where R^3 is phenyl, substituted phenyl, heteroaryl, substituted heteroaryl;

wherein said heteroaryl radical is a 5-6 membered ring

25 which can contain 1-4 nitrogen atoms, one oxygen or sulfur atom, or combinations thereof with 1 to 2 nitrogen atoms, and wherein phenyl and heteroaryl can be substituted with one or more of C_1-C_4 alkyl, C_1-C_4 alkoxy, chloro, fluoro, 30 trifluoromethyl, hydroxy, nitro, mono- and di- C_1-C_4 alkylamino.

56. A compound of Claim 1 of the formula:

- 350 -



wherein

R is selected from hydrogen, methyl or ethyl; the dashed lines a and b, indicate double bonds which can be present providing that when b is present, the 5 α hydrogen, Ha is absent;

Z can be

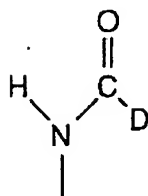
- 1) oxo,
- 2) α -hydrogen and a β -substituent selected from: C₁-C₄ alkyl, C₂-C₄ alkenyl, CH₂COOH, hydroxy, carboxy, COOC₁-C₄ alkyl esters, OCONR¹R², where R¹ and R² are independently H, C₁-C₄ alkyl, phenyl, benzyl, and R¹ and R² together with the nitrogen can form a 5-6 membered saturated heterocyclic ring, optionally with one other heteroatom; OC₁-C₄ alkyl, OC₃-C₆ cycloalkyl, -OCOCH₃, halo, hydroxy C₁-C₂ alkyl, halo C₁-C₂ alkyl or trifluoromethyl;
- 3) =CH-R' where R' is H, C₁-C₄ alkyl;
- 4) spiro:



where:

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A is (a):



5

D is R^1 or OR^1 ,
 10 where R^1 is: C_1 - C_{10} alkyl,
 C_3 - C_{12} cycloalkyl,
 C_6 - C_{10} aryl, or
 C_7 - C_{11} aralkyl with the proviso that when D is R^1
 and Z equals β -methyl, the value of C_1 - C_{10}
 15 alkyl is excluded;

O
 (b) $-\text{C}-\text{OC}_1-\text{C}_{12}$ alkyl, providing Z is not methyl;

20

O
 (c) $-\text{C}-\text{NR}_1\text{R}_2$, where R_1 and R_2 are independently H,
 C_1 - C_8 alkyl, providing Z is not methyl.

57. A compound of Claim 1 of the following
 structure:

25

4,7 β -Dimethyl-4-aza-Androst-5-en-3-one-17 β -ol, t-
 butyldimethylsilyl ether,

4,7 β -Dimethyl-4-aza-Androst-5-en-3-one-17 β -ol,

30

4,7 β -Dimethyl-4-aza-androstan-3-one-17 β -ol,

17 β -Pivaloyloxy-4,7 β -Dimethyl-4-Aza-Androstan-3-one,

17 β -Methoxycarbonyl-4-methyl-4-aza-androst-5-en-,7-dione,

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17 β -Amino-4,7 β -dimethyl-4-aza-5 α -androstan-3-one,

5 17 β -(1-Adamantyloxy)carbonylamino-4,7 β -dimethyl-4-aza-5 α -
androstane-3-one,

17 β -benzoylamino-4,7 β -dimethyl-4-aza-5 α -androstane-3-one,

10 7 β -Acetoxy-17 β -carbomethoxy-4-methyl-4-aza-5 α -androstan-3-
one,

17 β -(1-adamantyl)carbonylamino-4,7 β -dimethyl-4-aza-5 α -
androstane-3-one,

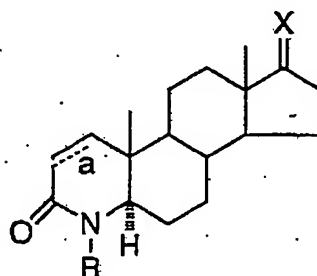
15 17 β (N,N-diisopropyl)carboxamido-4-methyl-4-aza-5 α -androstan-
3,7-dione

17 β -Benzyloxycarbonylamino-4,7 β -dimethyl-4-aza-5 α -androstan-
3-one.

20

58. A compound of the formula:

25



30

wherein:

Alk is C₁-C₄ straight or branched chain alkyl; dashed line a
can represent a double bond when present;

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R is selected from hydrogen, methyl or ethyl;

X is selected from O, NH, NR^a, wherein R^a can be OH, NH₂,
NHR¹, NR¹R², where R¹ and R² are independently
selected from C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl and C₆₋₁₂ aryl.

59. The compound of Claim 56 of the formula:

4,7β-dimethyl-4-aza-5α-androstan-3,17-dione,

17-oximino-4,7β-Dimethyl-4-aza-5α-androstan-3-one.

60. A method for treating the hyperandrogenic conditions of acne, androgenic alopecia, male pattern baldness, female hirsutism, benign prostatic hyperplasia, prostatitis, treatment and prevention of prostatic cancer, comprising administering to a patient in need of such treatment a therapeutically effective amount of the compound of Claim 1.

61. The method of Claim 57 wherein said compound is a 5α-reductase 1 inhibitor.

62. The method of Claim 57 wherein said compound is a 5α-reductase 2 inhibitor.

63. The method of Claim 57 wherein said compound is a dual inhibitor for both 5α-reductase 1 and 2.

64. A pharmaceutical composition comprising a therapeutically effective amount of the compound of Claim 1 in a pharmaceutically acceptable vehicle therefor.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 93/04643

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07J73/00; A61K31/58; C07J51/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07J ; A61K	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	JOURNAL OF MEDICINAL CHEMISTRY vol. 29, no. 11, November 1986, WASHINGTON US pages 2298 - 2315 G. H. RASMUSSEN ET AL 'Azasteroids: Structure Activity Relationships for Inhibition of 5-alpha-Reductase and of Androgen Receptor Binding'	1,64
Y	see page 2305 compounds 68 and 69, table V ---	1,64
X	STERIODS: STRUCTURE, FUNCTION, AND REGULATION vol. 47, no. 1, January 1986, STONEHAM, MA US pages 1 - 19 J. R. BROOKS ET AL '5-alpha-Reductase Inhibitory and Anti-Androgenic Activities of Some 4-Aza-Steroids in The Rat'	1,64
Y	see page 11, compound 52 ---	1,64
-/--		
¹⁰ Special categories of cited documents: ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "A" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
23 AUGUST 1993	06.09.93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	WATCHORN P.W.	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claims No.
X	US,A,4 377 584 (D. B. R. JOHNSTON ET AL) 22 March 1983	1,64
Y	see column 13; example 26 -----	1,64
Y	EP,A,0 414 529 (SMITHKLINE BEECHAM CORP.) 27 February 1991 see the whole document -----	1,64

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 93/04643

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 60-63 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9304643
SA 74295

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 23/08/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4377584	22-03-83	AU-B- 527030	10-02-83
		AU-A- 4569779	18-10-79
		CA-A- 1142914	15-03-83
		EP-A, B 0004949	31-10-79
		JP-C- 1511267	09-08-89
		JP-A- 54145669	14-11-79
		JP-B- 63061315	28-11-88
		JP-C- 1621732	09-10-91
		JP-B- 2046566	16-10-90
		JP-A- 63152320	24-06-88
EP-A-0414529	27-02-91	US-A- 5032586	16-07-91
		AU-A- 6115290	28-02-91
		CA-A- 2023609	25-02-91
		JP-A- 3118326	20-05-91